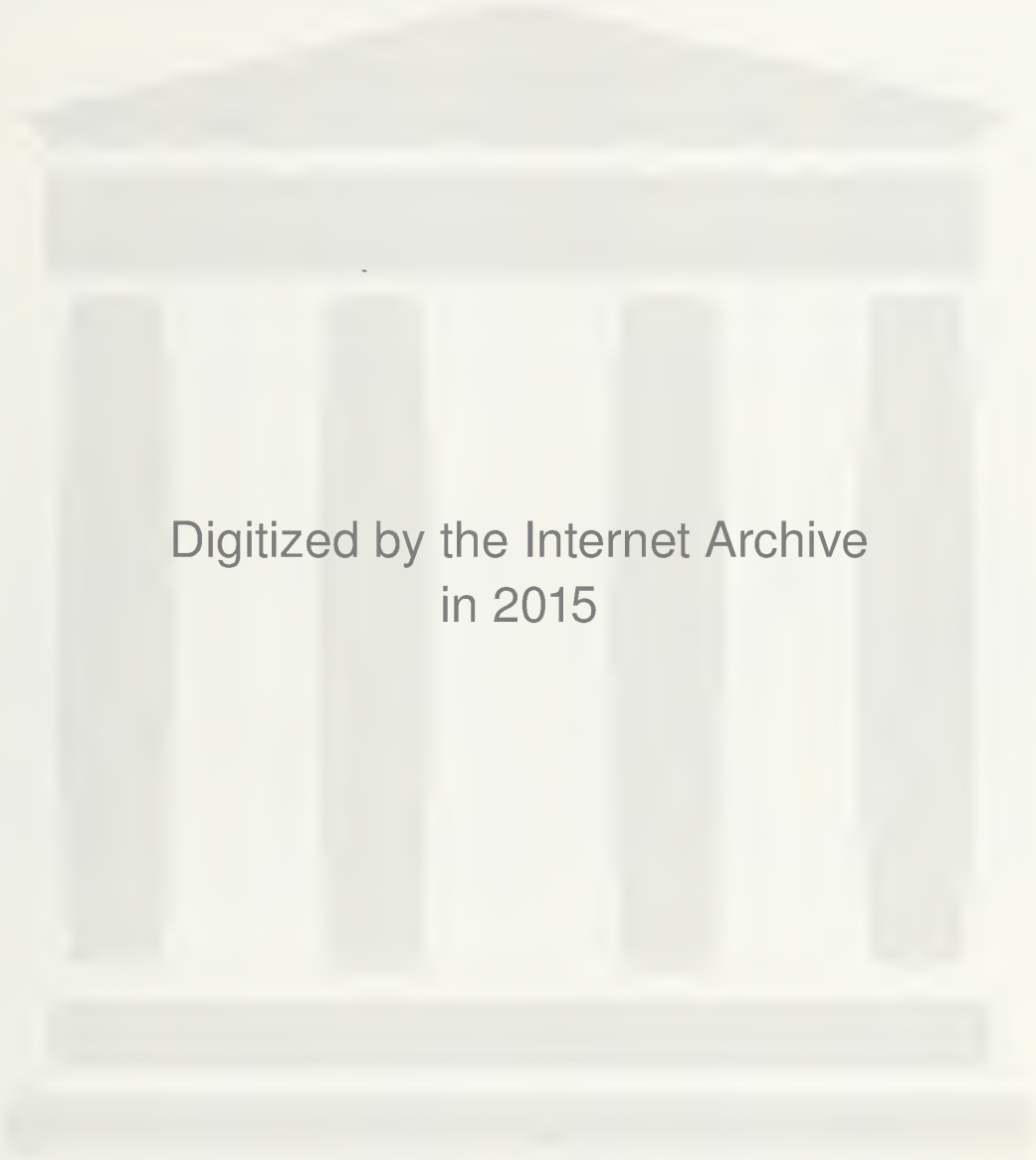
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Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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California Medicine
THE WESTERN JOURNAL OF MEDICINE

Phenothiazine Poisoning

A Review of 48 Cases

Daniel Barry, b.a., Frank L. Meyskens, Jr., m.d., and Charles E. Becker, m.d., *San Francisco*

■ *Of 48 cases of phenothiazine poisoning that were analyzed, 34 were attributed to suicide attempts, nine to accidental ingestion, and five to drug reactions.*

As outpatient treatment of schizophrenia increases, cases of overdose with phenothiazine drugs may be expected to increase also.

The prescribing of multiple phenothiazines and antidepressants is probably contributory to the occurrence of mixed drug ingestions.

The symptoms and signs of phenothiazine poisoning are largely predictable if the atropine-like, alpha-blocking, quinidine-like, and extrapyramidal actions of phenothiazines are appreciated. Unexplainable tachypnea and paradoxical miosis were noted in severe cases.

In one case in the study phenothiazine intoxication was present in the newborn infant of a schizophrenic mother.

Phenothiazines are becoming household drugs in California. The closing of state hospitals with the concomitant institution of mass outpatient treatment of chronic schizophrenics through community mental health centers, and recent questionable advertising campaigns advocating phenothiazines for the treatment of a wide variety of ailments have made these drugs generally available. The high incidence of schizophrenia in young adulthood and the increasing suicide rate in this age group[1] suggest that phenothiazine poisoning will become increasingly common. Two large literature reviews of psychotropic overdose have appeared recently, but the cited case studies were small and seemed largely to involve only severe ingestion illness.[2,3] An examination

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Submitted June 14, 1972.

At the time of this study Mr. Barry and Dr. Meyskens were third and fourth year students respectively attending the University of California, San Francisco.

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of the problem of phenothiazine overdosage was therefore undertaken. To that end the presentation, management, and outcome of 48 consecutive cases of phenothiazine poisoning were retrospectively analyzed.

Clinical Material

San Francisco General Hospital, a 1200-bed facility affiliated with the University of California Medical Center, recently instituted a computer card index according to final major diagnosis of all admissions. All charts (except two which were unavailable) coded under "tranquilizer toxicity" from October of 1969 to May of 1971 were studied, and 48 cases involving phenothiazine overdosage as the major contributing event leading to admittance to hospital were selected for further analysis. Included in the cases studied were suicide attempts, accidental drug ingestions, and serious drug reactions. The charts were analyzed for recorded drug type and amount, sex, age, race, marital status, vital signs, eye signs, mental status, treatment, complications, and length of stay. Since many charts were incomplete, complete information was not available on every patient. Because definite toxicology reports were generally not recorded, objective confirmation of the history was often impossible. In all four cases in which it was done, Phenostix testing of the urine was positive—in one case after dilution of the urine.

Results

Sociology (Table 1). Suicide gestures were most common in single, young, white women. Multiple drug ingestion was common (15 of 34 cases). Accidental ingestion seemed to involve the non-white community disproportionately. Phenothiazines of many varieties were involved (Table 2).

Vital signs (Table 3). Phenothiazine poisoning is characterized by a tendency toward hypothermia, tachycardia, tachypnea, and decreased diastolic blood pressure.

Mental status (Table 4). A clear tendency toward greater obtundation was noted in cases of mixed drug overdoses.

Eye signs. No trend was noted in the mixed drug overdoses. However, in the 12 reported cases of pure phenothiazine overdoses in which information was available (the more serious in-

TABLE 1.—*General Data on 48 Cases of Phenothiazine Poisoning*

	Suicide Attempts		*Accidental Ingestions*
Total	34		9
single drug	19		7
multiple drug	15		2
Sex			
male	14		7
female	20		2
Race			
white	32		2
non-white	2		7
Marital Status			
married	5		—
single	29		—
Age (yrs)		Age (yrs)	
Less than 26	21	Less than 5	8
More than 26	13	More than 5	1

TABLE 2.—*Phenothiazines Involved in Overdoses*

*Phenothiazine**	*Phenothiazine only*	*With Other drugs***
Chlorpromazine (Thorazine®)	16	8
Trifluoperzine (Stellazine®)	4	7
Thioridazine (Mellaril®)	3	2
Promazine (Sparine®)	1	0
Unknown	2	0

*in amounts ranging from 200 to 500 mg

**included Elavil®4, alcohol2, Artane®2, Librium® and 16 other drugs in single instances

TABLE 3.—*Initial Vital Signs in 26* Cases of Overdose with Phenothiazine Only*

		No. of Patients		*No. of Patients*
Temperature	98° or less	10	99° or more	5
Pulse	70° or less	2	100° or more	10
Respiration	12° or less	0	25° or more	6
Blood Pressure				
systolic	110° or less	3	130° or more	4
diastolic	70° or less	12	90° or more	1

*Complete data absent in many cases

TABLE 4.—*Initial Mental Status of 43 Patients for Whom Data Were Available*

	comatose	*lethargic semicomatose*	*awake oriented*	*hospital stay (days)*	*intubation*
With phenothiazine only	2	14	10	2.2	0
With other drugs	5	9	3	2.8	6

gestions) pupil size in nine cases was "small" (3 mm or less). Only in three cases were the pupils greater than 4 mm in diameter.

Treatment

Treatment included administration of ipecac (15 cases), gastric lavage (nine cases), intravenous hydration (25 cases), and intravenous diphenylhydramine (Benadryl®) in three cases. Methylphenidate (Ritalin®) had been given to two children at other hospitals before they were transferred to San Francisco General. Interestingly intubation was not needed in any case in which only phenothiazine was ingested, but it was required in six cases of mixed overdose.

Prognosis

None of the 48 patients died and half of them needed less than 24 hours in hospital. The average stay of the other 24 was 3.4 days and the longest was 31 days. Potentially serious complications were noted in 17 of the 24 patients with the longer stay in hospital. (Tables 5 and 6).

Discussion

In addition to their antipsychotic activity, the phenothiazines possess significant anticholinergic, alpha-adrenergic blocking, quinidine-like and extrapyramidal activity.[4] The importance of these modes of action becomes evident in the phenothiazine-poisoned patient. Although unavailability of toxicological data prevented confirmation of the history and the ruling out of mixed, occult ingestions, which are known to occur frequently,[5] distinct trends were evident in the patients said to have taken only phenothiazines. The hypothermia, tachycardia, and decreased diastolic blood pressure can be directly attributed to alpha-blocking and anticholinergic effects. Hypothermia can be relieved by appropriate covering[6] while the decreased blood pressure, largely secondary to alpha-blockade, can be easily managed by putting the patient in the reverse Trendelenburg position, by volume expansion, or in more extreme cases by use of direct-acting alpha stimulators.[2-4,7] Epinephrine with its mixed alpha and beta effect and isoproterenol hydrochloride (Isuprel®) with its largely beta action are therefore contraindicated. The tachypnea noted in these cases has not been noted previously (see reference 4), and an explanation is difficult to formulate. Small pupil size noted in 75 percent of the patients who had taken only phenothiazine was a surprising finding, and it was observed only in the most severely poisoned. This phenomenon may represent an overriding of the atropinic effect by the alpha-blocking effect of phenothiazines and may serve as a clinical clue to the severity of the overdose. This important observation requires further confirmation.

Prolonged QT interval which reverted spontaneously was noted in three cases. Although this is not well documented, persistent widening and QRS changes apparently can be treated effectively with diphenylhydantoin (Dilantin®).[8] The increased incidence of sudden death in phenothiazine-treated patients may be related to this quinidine-like effect,[9] and certainly an initial cardiogram is indicated for all phenothiazine-

TABLE 5.—*Complications of Phenothiazine Overdose*

Phenothiazine	*Complication*	*No. of Cases*	*Previously reported incidence[3] (percent)*
Chlorpromazine (Thorazine®)	seizure	1	1.3
	prolonged QT interval	1	16*
	distended bladder	1	3
	aspiration pneumonia	2	—
Thioridazine (Mellaril®)	ataxia	1	11.8
	aspiration pneumonia	1	—
Prochlorpenajine (Compazine®)	ataxia-rigidity	1	33.4
Triflupromazin (Stellazine®)	athetoid movement	1	1.3
Unknown	rigidity	1	—
	prolonged QT	2	16

*As noted by David, Bartlett and Termoni[10]

TABLE 6.—*Phenothiazine Reactions*

Description of disorder	*Tranquilizer*
1) Respiratory depression in the newborn of a schizophrenic mother	Fluphenazine (Prolixin®)
2) Photosensitivity reaction-vessicles of hands and face	Chlorpromazine (Thorazine®)
3) Inability to open mouth after treatment of heroin withdrawal	Chlorpromazine
4) Drug fever (105°F), with history of allergy	Chlorpromazine
5) Cogwheel rigidity	Thioridazine (Mellaril®)

poisoned patients. Although it does sometimes occur, death is a rarity in such cases.[10] The low mortality rate may reflect at least in part a tendency to attribute late deaths to other causes. An analysis of potential complications as noted in this study might indicate much more frequent serious sequelae to drug ingestion than are generally reported in other studies.[11,12] It is of interest, however, that all patients with complications in the present study recovered.

Severe acute extrapyramidal disorders were rapidly reversed with Benadryl® in two of three patients, and this drug is clearly indicated in such situations.[3] The case of respiratory depression in a newborn secondary to phenothiazine treatment of a schizophrenic mother (Table 6) indicates that phenothiazines do cross the placental barrier. Similar, but few, cases have been noted previously.[13,14] The continued persistence of a movement disorder up to 12 months in those cases and the respiratory depression for several days (as occurred in the present case) is disturbing. These little-emphasized side effects of phenothiazines will undoubtedly play a larger role as more young women are treated as outpatients for schizophrenia. The age and sex distribution of patients in the present study in this regard is striking. The increased incidence of phenothiazine overdose in the last nine months of this study (29 cases) as compared with the first ten months (19 cases) is of related interest.

The medical treatment of phenothiazine poisoning was quite satisfactory. Ipecac has been shown to be effective in the presence of these antiemtics.[15] Lavage even long after ingestion is effective since (1) the atropinic effect of phenothiazines delays gastric emptying and (2) phenothiazines are water-soluble and therefore slowly absorbed from the gastrointestinal tract.[3] These two factors and the pronounced radiopacity and slow disintegration of most phenothiazine compounds[16] suggest that the diagnosis of phenothiazine ingestion can be made radiographically (see Figure 1).

It should be noted that dialysis is ineffective since phenothiazines are strongly protein-bound.[4] The use of methylphenidate (Ritalin®) in the treatment of phenothiazine poisoning seems ill-advised since it produces both alpha and beta stimulation[8] and in the presence of the alpha-blockade of phenothiazines would be expected to lower blood pressure. However, both of two patients who were treated with Ritalin® had increased blood pressures for their age upon admission to our hospital.



Figure 1.—Radiograph in a case of chlorpromazine (Thorazine®) ingestion. The patient, a 27-year-old woman, had never received radiopaque contrast material.

The high incidence of mixed drug reactions most likely reflects the prescribing habits of physicians. The efficacy of mixing tranquilizers or combining tranquilizers with antidepressants has not been borne out experimentally[17] and indeed may be extremely dangerous (see reference 3, p 96). The increased obtundation in the patients with mixed drug overdose in the present study was striking. The occurrence of aspiration in three cases and in both of two patients said to be taking alcohol is note-worthy for two reasons: (1) the incidence of aspiration should be reducible by attention to position, suction, and careful intubation and (2) since undoubtedly more than two of the 48 patients were taking alcohol, general physicians should be alert to this unreported but important association since alcohol is a synergistic depressant. Certainly, a quick way to identify what drugs have been swallowed would greatly help in the management of all poisoned

patients. A recognition system utilizing mass spectroscopy and a computer link-up is being actively developed at San Francisco General Hospital.

The high incidence of accidental ingestion in non-white children probably reflects poor health education in general. It is likely that the candy-like appearance of phenothiazines plays a role.

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Corrosive Injury to Oro-Pharynx and Esophagus

Eighty-Five Consecutive Cases

Martin Feldman, M.D., Albert B. Iben, M.D., and Edward J. Hurley, M.D., *Sacramento*

■ *In 85 consecutive cases of ingestion of caustic material, 70 patients had oral burns, 29 incurred esophageal burns, and in three esophageal stricture developed, requiring repeated dilatation. Management involves early endoscopy to determine the extent of mucosal injury, antibiotics to reduce local or mediastinal infection, and steroids to prevent the chance for esophageal stricture.*

In the past few years, crystalline and liquid drain cleaners have become widely used. Their unguarded and often ubiquitous presence in the household makes them very tempting to children. The result is a rising rate of ingestion of these corrosive household caustics. Swallowing them may cause not only immediate damage or death but may also entail life-long sequelae.

Eighty-five consecutive cases of caustic ingestion treated at the Sacramento Medical Center, a metropolitan general hospital, were reviewed. The series covered a five-year period beginning in 1967. Seventy of the 85 patients were 1 to 5 years old and 63 of them were under 3 years. None was younger than 1 year. There were no cases in the 6 to 15 year old group. Fifteen patients were older than 15 years, ranging upward to 51 years.

Readily available household caustics were the principal agents ingested. During the five years covered by this review, Drano®, a crystalline alkali cleaner with a sodium hydroxide concentration of 54 percent, was the damaging agent in 44 of the cases. Soluble lye such as Liquid Plumr®, with a sodium hydroxide concentration of 30.5 percent, accounted for 16 of the cases reported. In the remaining 25 cases, ammonium hydroxide and various household cleaners containing caustic material were reported.

The children were always brought to the emergency room by their mothers. Invariably it was the mother who discovered the misadventure and provided the initial clinical history. Eighty of the patients ingested the caustic material at home. The remaining five found it in the garage, yard, at a neighbor's home or at work. Fifty percent of the patients were given milk, water, vinegar or citrus juices in the period immediately following ingestion. Ninety percent of the patients were brought to the emergency room within one hour of ingestion and all arrived within two hours.

In 15 of the 85 patients no oropharyngeal abnormalities were noted on initial examination in the emergency room. However, a high level of suspicion of ingestion existed because of evidence of the caustic material found on their

From the Section of Thoracic Surgery, Sacramento Medical Center (Drs. Feldman, Iben and Hurley); and Section of Thoracic Surgery, University of California, Davis, School of Medicine (Drs. Iben and Hurley).

Submitted June 30, 1972.

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clothes or because of burns on the hands or face. In other cases, oropharyngeal lesions ranged from a few scattered areas of superficial mucosal erosion of the lips or tongue in 61 patients to deep and extensive destruction of the lingual, buccal and pharyngeal mucosa in nine cases.

In 78 of the 85 cases, direct laryngoscopy and esophagoscopy were performed within 24 hours. Twenty-nine of the 70 patients with oral burns had mucosal esophageal injury as well. These lesions varied from small circumscribed areas of superficial erosion to diffuse full thickness desquamation of the hypopharynx and esophagus. Correlation existed between the degree of oral and esophageal involvement. Of the nine patients with extensive burns of the oropharynx all had esophageal burns, six with deep circumferential and three with less severe esophageal damage. Only three patients with esophageal burns had no oropharyngeal burns. Esophagoscopic examination was not done in seven of the patients, for a variety of reasons. One of these seven was treated with steroids and antibiotics. Six were sent home without therapy within 72 hours after admission.

There were no complications associated with initial esophagoscopy when performed in the first 24 hours. Two instances of esophageal perforation occurred from subsequent instrumentation. In one patient requiring repeated esophagoscopy and dilatation the esophagus was perforated 3 cm above the diaphragm 73 days after the initial injury. The perforation was immediately detected and thoracotomy and primary esophageal repair were performed without problem. A second case of perforation occurred during repeat instrumentation 38 days after ingestion of the caustic material. This was in a 3-year-old girl who had severe and extensive oro-esophageal burns requiring repeated instrumentation. At the third dilatation a perforation of the cervical esophagus was noted immediately above the level of stricture. Drainage of the cervical mediastinum and gastrostomy were performed. There were no further difficulties and subsequently repeated dilatations were carried out.

Of the 29 patients in whom esophageal findings were noted, 25 later had repeat endoscopy. Four were lost to follow-up. In three of the 25, strictures had formed which required multiple admissions for esophageal dilatation. One was the previously mentioned 3-year-old and the other two were adults. The remaining 22 patients had no evidence of stricture on repeat examination.

Management

For all patients presenting at the Sacramento Medical Center with a history indicative of ingestion of caustic agents a complete history is taken and on physical examination special attention is given to the oro-pharynx. If there is any evidence or suspicion of ingestion, the patient is forthwith admitted to hospital. No antidotes or emetics are administered and lavage and nasogastric intubation is avoided. Attempt is made to find the container of the ingested material or some of the material itself for proper identification.

Esophagoscopy is done upon admission or not later than 24 hours following ingestion. Patients with obvious second or third degree oropharyngeal burns are immediately given antibiotics (ampicillin 40 mg per kg of body weight per day in divided doses) and intravenous steroids (methylprednisolone sodium succinate, 20 mg every 8 hours for patients under the age of 2 years or 40 mg every 8 hours for those over 2. If there are only minor burns or it appears unlikely that a caustic was actually swallowed, no medications are given before esophagoscopy. If there is no evidence of mucosal damage on endoscopy, the patient is discharged without further care. If mucosal burns are demonstrated, steroids are continued for a minimum of seven days. The antibiotics are discontinued at five days if the patient is afebrile. At the end of a week esophagoscopic examination is repeated. If all lesions have healed, antibiotics are discontinued and the dosage of steroids tapered. A barium swallow study for baseline purposes is obtained, and the patient is then discharged to be seen at monthly intervals. If eschar or granulation tissue is still present when repeat endoscopy is done, a switch is made from methylprednisolone sodium succinate intravenously to methylprednisolone acetate given intramuscularly, 4 mg per kg of body weight per week in two divided doses.

Therapeutic esophagoscopy and dilatation are performed thereafter as needed until healing is complete and deglutition is adequate. At such time, steroids are tapered off and barium swallow

studies are done at intervals of six weeks, three months, six months and one year to observe any late stricture formation.

Discussion

Alkali in the concentrations found in commercially available household cleaners acts on oral, pharyngeal, and esophageal mucosal membranes within seconds, causing coagulation of cell proteins. The extent and depth of the initial injury depend upon the concentration, quantity and duration of contact with it. The depth varies from superficial hyperemia to ulceration of the mucosa, with or without slough. Severe burns involve the periesophageal tissue.[1,2,3]

Spontaneous repair after such an injury begins with the appearance of fibroblasts on the third or fourth day and the development of collagen begins between the eighth and twelfth days. By the end of the third week, collagen fibers begin to contract, producing distortion and narrowing. With circumferential burns, the esophageal lumen can be severely compromised as scar contracture progresses. Subsequent replacement of the muscular layer by scar leads to disruption of normal peristaltic movements. After four or five weeks, the healing of a severe burn may distort and greatly narrow esophagus in untreated cases.

In the present study 55 of the 70 patients under the age of six years had oral burns, but only 18 had esophageal involvement also. Of the 15 patients aged 16 and over, all had oral burns but only 11 had esophageal burns. The primary reason for this variance is the fact that most children spit out caustic material immediately upon tasting it, whereas adults bent on suicide deliberately try to swallow it.

The main causative agent in our series was a dry granular form of lye, Drano®. Liquids such as Liquid-Plumr® penetrate tissues rapidly and cause extensive damage in a much shorter time than dry lye. Hence, there is a greater chance for esophageal as well as oro-pharyngeal burns with liquid agents. In the present series and in others only 10 to 25 percent of patients who ingested granular lye had serious esophageal burns, against more than 50 percent of those who swallowed liquid lye.[5,6,7]

Sobell[8] pointed out that the typical poisoning of children occurs while the mother is in the immediate proximity or at least in the home. Our series confirms this finding. Sobell also noted that he could identify no relationship between the incidence of childhood poisoning and the storage practices of the families involved. One can only conclude that the very presence of any toxic agent in the home constitutes an attraction and consequently a threat, the magnitude of which depends upon the age and ingenuity of the child.

Baltimore[9] reached some interesting conclusions pertaining to parental knowledge of potential toxicology of common household products. In interviewing mothers of both poisoned and unpoisoned children, he found their knowledge of immediate treatment of the ingestion of toxics to be very good. Also, most of the mothers felt they had taken reasonable measures to keep these agents away from their children. In our series, approximately 60 percent of the mothers followed the instructions on the American Medical Association "poison chart." They did not attempt to induce vomiting and give emetics. They did give milk, citrus fruit juices or vinegar. In all cases, the child was brought almost immediately to the emergency room.

Unlike Yarington who reported[10] that histories provided by mothers in his series were "invariably inaccurate," we found the mothers' information highly reliable. However, because of three instances in which the ingested material turned out to be something entirely different than was initially reported, we always ask to see the container of the material involved.

Hollinger and others[2,6] oppose early esophagoscopy when lye burns are suspected because of the risk of esophageal perforation. However, the complication is infrequent. In Alford's[11] series of 69 cases in which esophagoscopy was performed soon after caustic ingestion was diagnosed, there were no complications. Yarington[12] had no complications in his series of 70 patients. In our series there was no morbidity associated with the initial endoscopy in the 78 patients. The esophagoscope should be passed only as far as the first identifiable mucosal lesion and not beyond. Daly[13] reported three perforations in 105 esophagoscopic examinations and stated that "none of these would have occurred if the esophagoscope had not been passed beyond the first burned area." The two perforations in our series occurred during subsequent instrumentation several weeks later. The patients in both cases had

complicated esophageal stricture requiring therapeutic rather than diagnostic esophagoscopy.

Following Spain's report[14] that the early administration of cortisone had an inhibitory effect upon the formation of granulation tissue and the fibroblastic reaction, Rosenberg[15] experimented with cortisone after induced lye burns in the esophagus of rabbits. He noted a significant decrease in the fibroblastic response and, subsequently, decreased scar formation and stenosis. At first, infection developed as a concomitant of the administration of steroids in these experiments, but this was subsequently overcome by giving penicillin at the same time.[16] Weisskopf[17] and later Johnson,[18] performing similar experiments in dogs, found that stricture did not develop in any of the steroid-treated animals, whereas all of the controls had stricture after 35 days. Weisskopf also made the important observation that unless steroids were given within 48 hours they did not prevent the formation of granulation tissue.

As a result of these experiments, several clinicians began to employ steroids in the treatment of caustic burns of the esophagus. Ray and Morgan,[19] using steroids and antibiotics, found stricture development in only one of eleven patients. Twenty-three patients were treated by Cleveland,[20] and stricture developed in five. Middlekamp[7] noted stricture formation in three of 21 patients treated with steroids and antibiotics, and all three had third degree esophageal burns. In Cannon's series of 59 patients with corrosive esophageal injury, stricture developed in three while receiving steroids. In our series, three of 29 patients with esophageal burns developed strictures. The stricture rate in all series reviewed appears to be between five and 15 percent in patients treated with steroids. Alford[11] reported stricture in 17 cases of 32 cases of caustic burns of the esophagus but none of the patients were treated with steroids.

It is important to note that for steroids to be fully effective, they must be started as soon as possible after the initial injury. In patients with extensive oropharyngeal involvement and strong probability of esophageal injury, steroids should be started immediately regardless of when esophagoscopy is to be done. The risk of stricture formation far exceeds any possible complications of a short course of steroids. In this series methylprednisolone sodium succinate and methylprednisolone acetate were used because of their rapid absorption and elimination, high blood levels, potent anti-inflammatory activity, and relative absence of side effects.

Because of the presence of necrotic tissue, breakdown in the esophageal mucosal barrier and use of steroids, simultaneous antibiotic therapy is essential. In this series, ampicillin was the drug of choice because of its highly effective action against the oropharyngeal flora.

Trade and Generic Names of Drugs

Solumedrol® methylprednisolone sodium succinate
Depomedrol® methylprednisolone acetate

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Uncomplicated Male Gonorrhea—A Review

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VENEREAL DISEASE is California's major communicable disease (Table 1) and gonorrhea is the leading reportable disease for 1971 (Table 2). The reported cases of gonorrhea in California and the United States have continued to increase at a high rate, but a slight decline has been recorded for California in 1971 (Table 3). However, adding unreported cases throughout the United States to those reported by physicians, one finds the estimated incidence of gonorrhea is approximately two million cases per year.[1] In 1970, a survey was conducted by the National Disease and Therapeutic Index of a representative sample of more than 1,500 private physicians. The findings were startling. Patients with gonococcal infections represented more than half of all venereal disease visits during 1970. Patient visits were mostly by males, 69 percent.[2] Thus, an epidemic of gonorrhea prevails.

Signs and Symptoms

The gonococcus, in the majority of cases, gains entry into the body by way of the genital tract. Less frequent sites of initial infections are the conjunctivas and rectal mucosa. The type of mucosa found in a particular part of the genitourinary tract basically determines the susceptibility of that tissue to gonococcal infection. Stratified squamous epithelium, which covers the external genitalia, extends for approximately 2 cm into the male urethra and is not susceptible to infection. Columnar epithelium, which lines the anterior urethra, urethra glands, prostatic ducts and prostate, seminal vesicles, vas deferens and epididymis, furnishes fertile soil for growth of the gonococcus. Transitional epithelium which lines the posterior urethra and the bladder is also susceptible to invasion by gonococci.[3]

Following the gonococcal infection of the genital tract, the incubation period is usually two to eight days, and the average is from three to five days. (However, the incubation period may be quite long, and several weeks can elapse before the patient notices any symptoms).

The initial symptom of gonorrhea in males is most often acute anterior urethritis, manifested

TABLE 1.—*California's Major Communicable Diseases, 1971*

	Reported Cases
Venereal Disease	114,000
Streptococcal infection	31,000
Hepatitis	11,000
Mumps	8,000
Rubella	8,000
Tuberculosis	4,000

Source: "California Morbidity," 1/7/72. California State Department of Public Health.

TABLE 2.—*California's Leading Reportable Diseases, 1971*

	Reported Cases
Gonorrhea	102,000
Streptococcal infection	31,000
Syphilis	12,000
Hepatitis	11,000
Mumps	8,000
Rubella	8,000
Tuberculosis	4,000

Source: "California Morbidity," 1/7/72. California State Department of Public Health.

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TABLE 3.—*Trends in Reported Civilian Cases and Rates of Gonorrhea per 100,000 Population*

United States and California, Fiscal Years 1968-1971

	1968		1969		1970		1971	
	Cases	*Rate*	*Cases*	*Rate*	*Cases*	*Rate*	*Cases*	*Rate*
United States*	431,380	219.2	494,227	245.9	600,072	292.7	624,371	304.6
California**	76,020	380.1	90,029	453.4	103,429	517.5	101,650	509.4

Source: *U.S. Public Health Service
**California State Department of Public Health

by a purulent urethral discharge and burning on urination. The discharge is most commonly yellow or brown; the meatus is red and edematous; and the urethra may be thickened and tender. Frequency, urgency and nocturia do not occur unless the posterior urethra and prostate gland become involved.

Acute prostatitis with the accompanying involvement of the seminal vesicles will cause fever, urinary symptoms, and frequently pain as well, generally deep-seated in the perineal region but often noted in the suprapubic or inguinal area or even in the sacral and lower lumbar areas.

An even more distressing involvement is that of acute epedidymitis. This is marked by pain in the scrotum (frequently wrongly attributed at first to orchitis or torsion) swelling and fever. With some exceptions this complication is associated with prostatitis as well.

Diagnosis

The presence of Gram-negative intracellular diplococci in a smear of the urethral exudate of a male patient, associated with typical clinical symptoms, is virtually diagnostic. If the smear examination does not reveal the organism, culture specimens must then be taken from the anterior urethra and inoculated on Thayer-Martin selective medium for laboratory cultivation.[4] The combination of a positive oxidase reaction of colonies and Gram-negative diplococci grown in the medium provides sufficient criteria for a diagnosis of gonorrhea. In homosexuals, a culture specimen should be taken from the anal canal and pharynx.[5]

The sending of urethral specimens taken in a private physician's office or a clinic to a distant laboratory has now been improved by the development of a new transport medium, Transgrow®, which is a modified Thayer-Martin antibiotic selective medium.[6] Transgrow medium is in an atmosphere of 10 percent carbon dioxide and 90 percent air; the medium is further enriched by increasing the agar content to 2 percent and the dextrose content to 0.25 percent.

It is well for the physician to keep in mind that gonorrhea may go unrecognized. Subacute or completely asymptomatic infections have evaded detection. Asymptomatic gonorrhea in males has been further substantiated by recent studies of Thatcher, et al.[7]

Gonococcal urethritis in men must be distinguished from nonspecific urethritis, which is not a single disease entity but a symptom of many diseases, including those caused by the mycoplasma organisms.[8] With mycoplasma urethritis, which may or may not be associated with intercourse, the incubation period is highly variable and usually prolonged. The urethral discharge tends to be scant, white and mucoid. On smear, miscellaneous organisms are present, while on culture there is no growth of Neisseria gonorrhoeae. The response to treatment is rather disappointing.

Therapy

Aqueous procaine penicillin G, 2.4 million units, intramuscularly, in one session, has been the treatment of choice in male gonococcal urethritis. This has been reiterated in studies performed by the Alameda County Health Care Services Agency,[9,10] including cooperative clinic studies conducted in venereal disease clinics throughout the United States.[11] However, with the increased resistance of the gonococci, the United States Public Health Service is now recommending that 4.8 million units of aqueous procaine penicillin G be given intramuscularly, in one session, preceded by one gram of probenicid by mouth, preferably at least 30 minutes before the injection.[12]

Over the years, Neisseria gonorrhoeae has

become increasingly resistant to penicillin.[13-15] However, this resistance is relative, not absolute. Studies of Cave and associates[16] further substantiated this; they found that a high proportion of strains were relatively resistant to penicillin G, but none of the strains were absolutely resistant. Similar findings have been reported in Europe.[17]

Recently, the Center for Disease Control, United States Public Health Service, released its latest findings concerning the bi-annual penicillin susceptibility testing program of gonococcal isolates.[18] The 2,117 cultures studied before 1971 indicated a trend toward increased resistance to penicillin. However, "preliminary data from susceptibility testing of 739 cultures isolated during 1971 suggest the upward trend in penicillin resistance may be leveling off."

Therefore, currently, most gonococci are still sensitive to the levels of penicillin achieved by one dose therapy. But it must be emphasized that the antibiotic must be given in adequate dosage, and at the same time it should be stressed that suboptimal doses must not be used.

Alternative Therapy

Tetracycline is an acceptable alternate antibiotic if the patient has allergic reaction to penicillin or the organism is resistant to it.[19,20] Treatment regimen in males is an initial oral dose of 1.5 grams followed by 0.5 gram orally every four to six hours for a total of 9 grams. (A recent study in our clinic, not yet published, has established a 95 percent cure rate in men receiving an initial oral dose of 2.0 grams of tetracycline hydrochloride and followed by 0.5 gram every four to six hours for a total of 7.5 grams). Doxycycline and ampicillin are also effective in recommended dosages.[21,22] (Of course, ampicillin cannot be utilized for the penicillin-allergic patient). However, increased resistance to these antibiotics as well as to tetracycline is a matter of continuing concern. Furthermore, strains relatively resistant to penicillin also tend to have diminished susceptibility to these other drugs.[23,24]

Excellent results have been obtained by combining procaine penicillin G, 2.4 million units, with the administration of 1.0 gram of probenecid given orally one hour before the injection. Similar results have also been reported with ampicillin sodium, 2 grams, preceded by 1.0 gram of probenecid given orally one hour before injection.[25] (The use of probenecid inhibits the excretion of penicillin and ampicillin; therefore, the antibiotic reaches higher serum levels which are maintained for a long period).

A new drug, spectinomycin hydrochloride, has recently been licensed in the United States for treatment of only gonorrhea. A 2.0 gram intramuscular injection, in one session, has proven most effective in males.[26,27] However, it must be kept in mind that spectinomycin is recommended as an alternate antibiotic to penicillin, not as the drug of choice, for male gonorrhea.

Follow-Up

The importance of follow-up examination needs to be stressed to the patient. A test of cure should be routine. Follow-up cultures are essential for the immediate detection of treatment failure, since we know that symptoms may be completely suppressed by suboptimal therapy.

At times it is difficult to distingiush between treatment failure and reinfection, for the incubation period is short and effective immunity is lacking. Clinical symptoms at follow-up two to five days following therapy may be due not to treatment failure but to reinfection, especially if the patient has had sexual re-exposure to his untreated sex contact ("ping-pong" disease). Retreatment generally consists of doubling the initial therapeutic dose, in one session.

Concurrent Syphilis

The gonorrhea patient should also be assessed for syphilis, including a serologic test, for it is possible for both diseases to be present in the same patient. If infectious syphilis is diagnosed, either on the basis of a reactive serologic test or a lesion positive on darkfield examination, the standard treatment for syphilis must be given simultaneously with the treatment for gonorrhea.

A recent study by the United States Public Health Service[28] indicates that aqueous procaine penicillin G in doses of 2.4 or 4.8 million units, intramuscularly in one session, is effective therapy for *incubating* syphilis. Therefore, the investigators point out, "Patients with gonorrhea who have been named as contacts of persons with infectious syphilis and are treated with these schedules do not need additional therapy with penicillin G benzathine. It should be emphasized that such patients should receive a thorough

physical examination, including darkfield examination of all suspicious lesions and serologic tests to rule out syphilis before gonorrhea therapy is instituted . . ." These results permit a modification of the long recommended practice of following gonorrhea patients with three monthly serologic tests for syphilis. Furthermore, patients with confirmed gonococcal urethritis who have been treated with 2.4 or 4.8 million units of aqueous procaine penicillin G, intramuscularly in one session, also no longer need to be followed with serologic tests.

A word of caution about tetracyclines: Tetracycline may be effective in syphilis if it is administered over a prolonged period and in adequate dosage. However, the short treatment schedule prescribed in gonorrhea is not adequate to abort all cases of incubating syphilis; hence, gonorrhea patients treated with tetracycline must continue to receive adequate serologic follow-up.

Summary

Although the clinical signs and symptoms of gonorrhea in males are usually specific and somewhat pathognomonic in uncomplicated cases, definitive diagnosis can only be based on a Gram-stain smear; subsequent cultures are also indicated in some cases.

The drug of choice is still intramuscular aqueous procaine penicillin G. Although penicillin resistance is well established, this is relative and not absolute. Follow-up examinations should be routine on all patients. Cultures provide an immediate detection of all therapeutic failures. Retreatment, of course, is mandatory to prevent the spread of resistant strains.

In all instances of gonorrhea in males, the possibility of concurrent syphilis must be considered. Current research indicates that the use of procaine penicillin G eliminates *incubating* syphilis as well, which reinforces the case for penicillin as the drug of choice.

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Medulloblastoma—Treatment and Prognosis

A Study of Seventeen Cases in Ten Years

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■ *In a series of 17 biopsy-proved cases of medulloblastoma all patients were treated by megavoltage irradiation in the Stanford University Division of Radiation Therapy. The entire craniospinal axis was treated in each case. The five-year survival in the series was 27 percent.*

Two ten-year survivors were studied in detail. The major long-term disability was inhibition of growth of the vertebral column.

In this series, a normal tissue nominal standard dose of at least 1275 rets was necessary for tumor control.

MEDULLOBLASTOMA HAS BEEN regarded as having a poor prognosis. Cushing,[1] in a surgical series of 61 cases had an operative mortality of 32 percent and was left with only one patient alive at three years. Almost half of the patients received limited postoperative irradiation, but irradiation of the whole ventricular system and spinal cord was not performed. Paterson and Farr,[2] in 1953, reported seven of thirteen children alive at three years after treatment of the whole of the cerebrospinal axis by irradiation. Smith[3] reported 28 percent of 38 patients alive at five years, and Bloom[4] reported 32 percent of 68 patients followed for five years alive, and 26 percent of 34 cases followed for ten years alive. In both of these series irradiation was given to the whole of the cerebrospinal axis.

In the etiology of medulloblastoma it is postulated that primitive cells found in the region of the posterior medullary velum may, under certain conditions, undergo malignant change. In children medulloblastoma is usually a midline lesion, while in adults it is often placed more laterally. Because of its better prognosis and amount of reticulin fibers, in adults, it has been called an arachnoidal cerebellar sarcoma. Rubinstein and Northfield,[5] in a critical review, decided that medulloblastoma and cerebellar sarcoma were one and the same.

At Stanford, in the ten-year period from 1960 to 1970, 17 proved cases of medulloblastoma were treated in the Division of Radiation Therapy. There were 13 males and four females in this series, and the age range varied up to the age of 43, but the majority of patients were under 15 years at presentation. Table 1 shows the age distribution. The symptoms were all those of cerebellar dysfunction, and in most cases were

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TABLE 1.—*Age of patients treated with irradiation for medulloblastoma.*

Age	No. of Patients
0 – 5 yr.	5
5 – 10 yr.	5
10 – 15 yr.	3
27 yr.	1
31 yr.	1
35 yr.	1
43 yr.	1

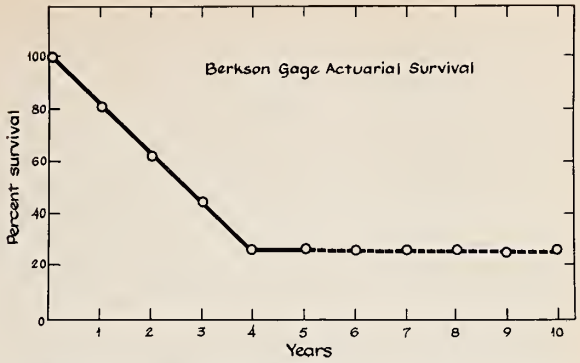


Chart 1.—Actuarial Survival. Broken line means insufficient data for significance.

of short duration. All patients had craniotomy and a minimum of biopsy. Four patients had complete surgical removal of the tumor before further definitive therapy. The technique of radiation therapy is one which is fairly standard in radiation therapy departments, and in it the entire cerebrospinal axis is irradiated, with the lower border of the radiation portal 2cm below S-2. A further boost is given to the area of the posterior fossa at the completion of the cerebrospinal irradiation. At Stanford, all patients have been treated by megavoltage radiation, at first using the 4.7 Mev Stanford Medical Linear Accelerator, and more recently with a 6 Mev Varian Linear Accelerator. The brain was treated with opposing lateral portals to a midplane dose of 4,000 rads in four weeks, and the spinal cord was given the same dose in the same period. A booster dose of 1,500 rads in a week and a half was given to the primary site of the tumor. The match line between the brain and the spinal portals was moved at weekly intervals so that the possibility of underdosage or overdosage of this region was diminished.

Of the 17 patients who completed radiation therapy in the ten years, ten are living. Five patients were treated more than five years ago, and of these two are alive. Chart 1 shows a Berkson Gage actuarial analysis. It is seen that there is a fairly regular attrition rate up to four years, after which the rate remains constant at 27 percent. We have, however, too few cases to make this of much significance for periods over five years. Of the four patients who were over 15 years old at presentation, three are still alive. The fourth died, without evidence of malignant disease, from viral pneumonia two months after therapy. Three of the four patients who had gross surgical removal of the tumor are well, two of them three years and the other one year after therapy. One died at one and a half years from recurrence of the disease in the original site. Two of the four female patients in the series are well. One died 18 months and one nine months after treatment, both with disease in the original site.

Three patients had retreatment for medulloblastoma after the initial treatment had failed. In each case the disease had recurred in the posterior fossa. Two died within four months of the completion of the second course of radiotherapy, and the third patient, who received a smaller dose of irradiation—2000 rads in two weeks—combined with vincristine (Oncovin®) and intrathecal methotrexate, in the retreatment phase, is disease-free three years later.

Metastasis, except in the cerebrospinal area, is rare, as with most other forms of malignant disease in the brain. One patient, however, had multiple bone metastasis, proved by biopsy, three years after the initial diagnosis. He did not respond to chemotherapy and died one year later.

The two patients who were treated more than five years ago were recently reviewed. Both were apparently free of disease and had little in the way of neurological dysfunction. One patient, a boy who was 17 months old when he presented with a medulloblastoma in June of 1961, was treated with a total of 4,500 rads in 38 days to the brain and the spine, and a booster dose of 500 rads was given to the posterior fossa. In November 1971, the patient was re-evaluated and the main abnormality was short stature. He was

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four standard deviations below the normal in height for his age and the spine was eight standard deviations below the normal size. The skull was one standard deviation below normal size but the limbs showed no diminishment in growth. Endocrinologically the patient was normal, growth hormone and thyroid-stimulating hormone being within normal limits for his age. He also had right amblyopia and slight cerebellar dysfunction. The other patient, a girl of 5, was treated in August 1961. She received 4,500 rads to the brain and the spinal cord, and an extra boost of 500 rads was given to the posterior fossa. The 4,500 rads was given over a period of 43 days. The patient was re-evaluated in July 1971. In height she was two standard deviations below normal, and at the age of 15 had the height average of an 11-year-old. The spine was four and a half standard deviations below normal and the limbs and skull were within normal limits. There were no abnormalities of the endocrine system, the patient menstruating normally and having normal thyroid-stimulating hormone levels, and there was no evidence of growth hormone deficiency. Her memory was poor and she had visual perception problems, making it difficult for her to read correctly. She was considered to be a borderline mental defective. Whether the defects in memory, visual perception and intellectual efficiency are the result of the tumor or of the irradiation is impossible to say, but the defect in height is certainly due to long-term damage from irradiation. There have been no other patients who have survived more than five years, and little is apparent in the way of growth retardation of the remaining patients.

Autopsy was done in three cases. One patient had received a second course of irradiation to the posterior fossa for recurrent disease and at autopsy was found to have medulloblastoma surrounding the whole of the brain and the spinal cord, together with radionecrosis of the cerebellum in the area which had been retreated. Another had extensive tumor throughout the brain and the spinal cord, with a large mass of tumor in the region of the posterior fossa. The third patient showed no evidence of tumor at autopsy, the reason for death being viral pneumonia.

In attempting to estimate the dose which these patients received to their brain and spinal cord, we used the concept of the nominal standard dose proposed by Ellis.[6] In this system, one is

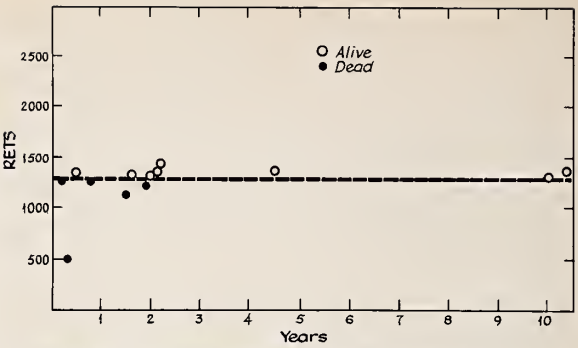


Chart 2.—Nominal standard dose ($D = N.S.D. \times N^{0.24} \times T^{0.11}$) for the brain and spinal cord.

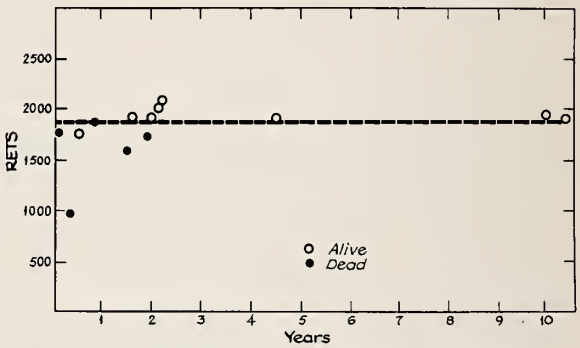


Chart 3.—Nominal standard dose ($D = N.S.D. \times N^{0.24}$) for the tumor.

able to compare different treatments which have been carried out over different periods of time and with a different number of fractions. One can convert the total radiotherapy dose received in each patient to a single dose which can be compared from one patient to another. The formulae used are $D = NSD \times T^{0.11} \times N^{0.24}$, and $D = NSD \times N^{0.24}$. The first formula is for normal tissues, and the second for tumors; the D is the total dose, the NSD is the apparent single or standard dose in rets, T is the time, and N the number of fractions.

Charts 2 and 3 show the doses with the patients in this series for both the normal tissue and the tumor. Four of the 17 cases are not included as there were many gaps in the treatment, making the calculation of the NSD too problematical. It is seen with the normal tissues formula that there are no failures if an NSD dose of more than 1,275 rets is given or with the tumor NSD a dose of 1,900 rets. For the posterior fossa, where a further booster dose has been given for all patients, it is difficult to adequately assess the minimum dose required, although it is probably in the region of 2,200 rets for the tumor. The interesting point is that using this system it is seen

that besides giving a total dose of at least 4,000 rads to the cerebrospinal axis, it is important that this dose is accomplished in four weeks, using four or five fractions of radiation per week. Should the treatment time be protracted because of nausea or lowering of the blood cell count, the treatment will probably fail unless slightly higher doses are given. Against this must be placed the fact that if high doses are given, damage will almost certainly be done to subsequent growth of the vertebrae, and probably the brain and spinal cord.

Discussion

The Stanford series agrees with most other published series, having a five-year cure rate of approximately 30 percent. A major sequelae in the Stanford series is the growth defect in the vertebrae. Amblyopia in one patient and mental retardation in another are other possible complications of treatment. Bloom found optic atrophy in five patients who survived for more than three years and he attributed this to the raised intracranial pressure at the beginning of therapy. Two of six of Bloom's patients who were under two years of age at presentation survived more than five years and both are demented. The growth defect noted in the Stanford series is particularly pertinent at this time when consideration is being given in many centers to irradiation of the whole of the cerebrospinal axis as part of the treatment of acute lymphoblastic leukemia. The dose given in acute lymphoblastic leukemia is only half of the dose required in medulloblastoma, but it is likely that growth in the vertebrae will be impaired.

The survival data were better for the older than for the younger patients in the Stanford series. Three of the four patients who were over the age of 15 at presentation were alive without disease at the time of this study. Gross surgical removal of the tumor also seems to give a better survival, three of the four patients in the Stanford series who had gross removal of the tumor being well and without disease.

It is difficult in this series to say whether failure in treatment occurred mainly in the posterior fossa or elsewhere in the cerebrospinal axis. Three patients were retreated for recurrence of disease in the posterior fossa and two died very shortly after retreatment. Autopsy showed extensive disease in both cases, not only in the posterior fossa but throughout the brain and the remainder of the spinal cord. This suggests that if disease recurs in the posterior fossa, it may be extending throughout the whole of the axis. The brain will not tolerate retreatment with 4,000 rads to the whole of the volume, and if further treatment is required a much lower dose of radiation therapy has to be given.

Distant metastasis is rare in medulloblastoma[7,8,9] but in the present series there was proved metastasis in bone, most of the bones being involved. The lungs were not involved. Rubinstein[7] noted that lung involvement is very rare.

The successful retreatment of recurrent medulloblastoma with low dose irradiation, intrathecal methotrexate and intravenous vincristine is worthy of note, and may point to a way to approach recurrent disease.

Whether the technique of delivering the radiation therapy can be improved is difficult to say. With the modern advent of neutron therapy and pi mesons, it is possible that more accurate dosage will be given to the spinal cord and the brain. However, a greater emphasis on good dosimetry with a realization that a minimum dose of approximately 4,000 rads in four weeks is required to control the tumor, seems to be one good way of improving the survival.

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Refer to: Rosenberg RN, Campbell J: Myasthenia gravis—University of California, San Diego (Specialty Conferences). Calif Med 118:18-23, Jan 1973

Specialty Conference

Myasthenia Gravis

Participants: Roger N. Rosenberg, M.D.,
James Campbell, Lt Comm, USN, MC

Taken from the weekly Pediatric Grand Rounds held at the University Hospital of San Diego County, University of California, San Diego, School of Medicine, June 20, 1972

Dr. Campbell:* The patient, a Filipina, was first seen at the U.S. Naval Hospital in San Diego in March of 1971, when she was 7 years, 3 months of age. At that time, she complained of diplopia. She had no other symptoms of weakness. There was no difficulty in swallowing and no weakness referable to muscles of the extremities.

Physical Examination

She was well developed, slender and intelligent. Neurological examination revealed bilateral ptosis and bilateral symmetrical ophthalmoparesis in all directions of gaze. She had diplopia on far lateral gaze bilaterally. Examination of the other muscle groups for tone, bulk, strength, and reflexes was entirely normal. She was given edrophonium chloride (Tensilon®) 0.1 cc (1 mg) intravenously and complete disappearance of ptosis and ophthalmoparesis followed. A diagnosis of juvenile myasthenia gravis was made.

The treatment of the patient was titrated to a dose of of 20 mg of pyridostigmine (Mestinon®) three times a day. Both the ptosis and the ophthalmoparesis responded well.

In May, 1971, the patient was again admitted because of a nasal quality to her speech, drooling, and dysphagia. The amount of pyridostigmine was increased to 60 mg every 8 hours. She did well for four weeks, but in June generalized weakness, abdominal pain and increased salivation developed. She was readmitted and placed on a respirator for 72 hours. On discharge she was given pyridostigmine 300 mg four times a day. In September of 1971 she was again admitted for respiratory insufficiency thought to be related to cholinergic crisis, and again was placed on a respirator. In September thymectomy was performed. After the operation she remained on a respirator for five days, and administration of pyridostigmine 30 mg every 5 hours and ephedrine sulfate 12.5 mg three times a day was begun again. Gross and microscopic examination of the thymus was entirely normal. In February, 1972, an influenza-like illness developed. At that time the patient was taking pyridostigmine 60 mg every 6 hours. On March 2, the body temperature rose to 40.6° C (105° F) respirations were shallow and the patient cyanotic. She was admitted to the U.S. Naval Hospital where tubes were placed and she was put on a respirator. Cardiac arrest occurred and all resuscitative measures were unsuccessful.

Autopsy revealed moderate lymphorrhage formation throughout the entire myocardium, and extensive infiltration was noted in skeletal muscle.

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Discussion

DR. ROSENBERG:* Myasthenia gravis is a neurological disorder of unknown cause in which there is weakness, especially of muscles innervated by cranial nerves, due to a neurophysiological impairment of neuromuscular transmission. The weakness is corrected by cholinergic drugs. The disease has been reported as occurring from the neonatal period through the ninth decade of life. Myasthenia gravis unassociated with a thymoma occurs most frequently in the third, fourth, and fifth decades of life in women and in the sixth and seventh decades in men. In contrast, myasthenia gravis associated with thymoma is most frequent in the sixth and seventh decades of life in both sexes. It is a disorder which occurs in children, and neonatal myasthenia occurs in about 10 percent of infants born of myasthenic mothers. Cases such as the one under discussion, that of a 7-year-old girl with seriously progressive myasthenia gravis, are seen with some regularity on neurological services.

The Myoneural Junction

The neromuscular junction is the anatomic site and a neurophysiological impairment in neuromuscular transmission is the basis for weakness in this disease. Thus, it becomes important to review the anatomic structures and the neurophysiology and biochemistry of events at the neuromuscular junction to relate them to myasthenia. The motor nerve axon develops into an expanded nerve terminal at the point of innervation with a voluntary striated skeletal muscle fiber, and in the presynaptic nerve terminal one can readily identify two important structures in electronmicrographs. The first are the 600 Å cholinergic vesicles containing between 10 and 50 thousand molecules of acetylcholine. The other important structure is the mitochondrion, which not only provides adenosine triphosphate (ATP) for energy for the biochemical processes of neuromuscular transmission but specifically is the site of the pyruvic acid dehydrogenase complex and acetyl-coenzyme A synthetase, two enzymes required for the generation of activated acetate or acetylcoenzyme A; this important precursor substrate is utilized with choline to generate acetylcholine presynaptically in the cytoplasm of the nerve terminal. The cytoplasmically synthesized acetylcholine is then taken up into the cholinergic vesicles for storage. When the motor axon is electrically depolarized, vesicle-stored acetylcholine is released by exocytosis through a series of biochemical steps which remain unknown. Free acetylcholine then transverses the 200 Å gap between the pre-membrane and post-membrane to arrive at the postjunctional membrane receptor site, depolarizing the membrane of the muscle fiber and generating a discrete muscle miniature end plate potential. Somewhere in this sequence of events in myasthenic patients there is a defect or defects which underlie the impairment in neuromuscular transmission.[1,2]

The mechanisms by which acetylcholine is stored in the synaptic vesicle are complex. The molecular defect in myasthenia may reside even within the vesicle itself. Information on the cholinergic synapse in the superior cervical ganglion of cats suggests that there is a readily releasable acetylcholine fraction, and that the acetylcholine that is snythesized last is released first. A depot pool of acetylcholine is then activated subsequent to the total release of the readily releasable fraction. There is also a stationary pool of acetylcholine which is even less accessible for release. Thus, it is possible that the molecular defect in myasthenia is in the activation of acetylcholine from one pool to the other within the nerve terminal. This would lead to an inability to release acetylcholine and make it unavailable to the postjunctional receptor site.

The biochemical events of acetylcholine synthesis and its storage in a vesicle might be entirely normal in myasthenia, and the impairment in neuromuscular transmission might result from impairment in the ability for acetylcholine to be retrieved from the cholinergic vesicle. It has been suggested that there is a specific mechanism by which the vesicle moves down from the depths of the nerve terminal toward the pre-junctional membrane and fuses with the plasma membrane of the nerve terminal. With fusion, the acetylcholine from the vesicle is deposited into the cleft between the pre-junction and the post-junction by a process referred to as exocytosis. It is possible that this series of steps might be impaired, either mobilization down toward the pre-junctional membrane of the vesicle, or impairment of fusion of the vesicle with the pre-junctional membrane and subsequent release of

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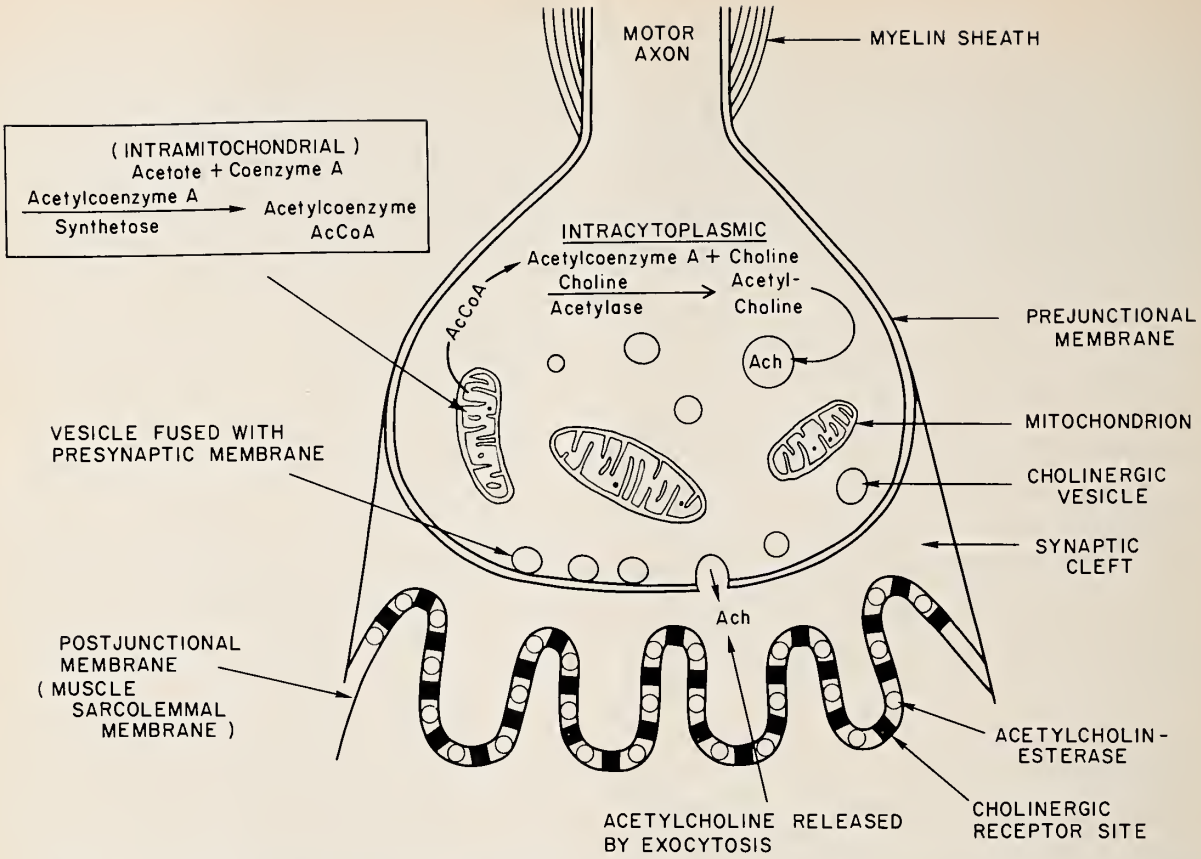


Figure 1.—The myoneural junction is illustrated indicating the important structures and sequence of events involved in the metabolism of acetylcholine.

acetylcholine. The impairment in neuromuscular transmission theoretically could result because of reduced availability of acetylcholine from impairment of any one of the steps mentioned.

The only biochemical steps in acetylcholine metabolism which are described in the normal neuromuscular junction are for its synthesis. This involves the generation of acetyl-coenzyme A from acetate, which is catalyzed by acetyl-coenzyme A synthetase, an intramitochondrial enzyme. This is followed by the choline acetylase reaction in which acetylcholine is synthesized from acetyl-coenzyme A and choline, and this occurs in the cytoplasm of the nerve terminal. Acetylcholine is then taken into the cholinergic vesicle and stored (Chart 1).

Effects of Acetylcholine on the Post-junctional Membrane

Acetylcholine results in the production of miniature end plate potentials (MEPPS) at the neuromuscular junction. The miniature end plate potential at the neuromuscular junction is analogous to the excitatory post-synaptic potential which occurs within the central nervous system. Miniature end plate potentials are produced by the quantal release of acetylcholine. The dogma is that one vesicle contains one quantum of acetylcholine, and, when released and combined with the post-junctional membrane receptor site, produces a permeability change equivalent to one miniature end plate potential. Miniature end plate potentials then summate in time and space to produce the all-or-none propagated muscle action potential which then sweeps longitudinally across the sarcolemma muscle membrane and into the depths of the muscle via the transverse T-tube system. The normal miniature end plate potential is one millivolt. The myasthenic miniature end plate potential is approximately 0.2 millivolt. The frequency of occurrence of miniature end plate potentials in myasthenia is entirely normal.[2]

A reduced amplitude of a miniature end plate potential might result due to impaired rate of synthesis of acetylcholine relative to its utilization, impaired intake of acetylcholine into the cholinergic vesicle, impaired release of acetylcholine from the vesicle, inactivation of acetylcholine within the cleft between the pre-membrane and the post-membrane, or a decrease in sensitivity of the receptor site itself to acetylcholine. Further, small miniature end plate potentials might be produced because of abnormal synthesis of a false transmitter which competes with acetylcholine for the receptor site. It is also possible that the small miniature end plate potential results from increased activity of acetylcholinesterase, making less acetylcholine available to the adjacent receptor site. The mechanism of pathogenesis is unknown, but it is clear that we are dealing with a selective abnormality in one cholinergic synapse, the voluntary striated neuromuscular junction.

Clinical Manifestations

There have been several landmarks in our understanding of myasthenia since Sir Thomas Willis first described this disease in 1672.[3] In 1934, Mary Walker reported that myasthenia gravis resembled very much the clinical syndrome of curare poisoning, and she suggested that the use of anticholinesterase drug might be helpful in managing patients with myasthenia gravis, as it is in curarized persons. In 1941, Harvey and Masland reported the defect in neuromuscular transmission. Demonstration of the impaired neuromuscular transmission is a valuable clinical tool which can be used in the day to day evaluation of myasthenia. A stimulating electrode is placed on the nerve and a recording electrode on the muscle. The nerve is stimulated at 3 to 20 cycles per second, and the amplitude of the evoked muscle action potential is recorded with repetitive stimulation. In myasthenia there is a very profound, very quick fall-off in the amplitude of the evoked muscle potential with repetitive stimulation. This is the hallmark of the clinical diagnosis of myasthenia.[1] The improvement in amplitude of the muscle action potential with rest or the administration of an anticholinesterase drug is also a characteristic of this disease. Neurophysiological parameters correlate well with improved strength in a patient who receives an anticholinesterase drug. These events may occur quickly and dramatically following the administration of edrophonium choride (Tensilon®).

The involvement of musculature innervated by cranial nerves is common in myasthenia. Weakness of extraocular muscles, ptosis, facial weakness, a sneer instead of a smile, weakness on chewing and swallowing, and weakness of the extensors and flexors of the neck are common presenting manifestations in myasthenia gravis. Weakness of muscles innervated by cranial nerves is commonly seen in association with generalized weakness. To confirm that the occurence of this weakness is due to myasthenia, one should do the following: 1) perform a Tensilon test, using 10 mg to 15 mg of edrophonium chloride injected over a 90-second period and observe for a quick but transient improvement in strength; 2) determine if there is impairment in neuromuscular transmission by repetitive stimulation of a peripheral nerve and recording of the amplitude and frequency of the evoked muscle action potentials. The muscle tested, of course, should be a muscle which is clinically affected.

Treatment

Once the diagnosis of myasthenia gravis has been established, the patient should be treated with longer acting anticholinesterase drugs such as prostigmine or pyridostigmine. After the appropriate drug dosage has been achieved, the patient should again be rechallenged with a Tensilon test to see if that dose of anticholinesterase drug produces maximal effect. It should be emphasized that not enough acetylcholine at the receptor site results in weakness, as does too much acetylcholine.

The features differentiating myasthenic deterioration or myasthenic crisis from cholinergic deterioration or cholinergic crisis may be difficult to distinguish. The occurrence of salivation, small pupils, diaphoresis, goose bumps, abdominal cramps, and bladder cramps, associated with progressive weakness strongly indicates excessive acetylcholine. A Tensilon test performed in such conditions may be dangerous. The patient's muscle function can rapidly deteriorate to the point of respiratory insufficiency. If the patient is progressively becoming weaker without associated cholinergic autonomic manifestations and dra-

matically improves with Tensilon, it indicates the presence of myasthenic crisis or insufficient acetylcholine at the neuromuscular junction cholinergic-receptor site.

Pathogenesis of Myasthenia

What is the current information to indicate what the biochemical defect may be in this disease? It is possible that the impairment in neuromuscular transmission results from a hemicholinium-like defect. Hemicholinium is a choline analog which impairs the rate of synthesis of acetylcholine presynaptically by restricting the availability of choline through blocking its re-uptake. Hence a motor axon which is rapidly depolarizing and releasing acetylcholine may rapidly lose its capacity to synthesize acetylcholine at a rate commensurate with its needs. The second possibility is a botulinum toxin-like defect. Botulinum toxin is a very potent agent which prevents the presynaptic release of acetylcholine. Either drug would have the effect of reducing availability of acetylcholine to the cholinergic receptor protein. Acetylcholine may not be the only transmitter synthesized; a false transmitter might be synthesized and incorporated into the vesicle, displacing acetylcholine. When such a vesicle reached the prejunctional membrane, fused with it, and released its contents by exocytosis, it would release the competitive false transmitter as well. Thus, a false transmitter might impair neuromuscular transmission by inhibiting acetylcholine entry into the vesicle or competing with acetylcholine for the cholinergic receptor site post-synaptically. Another possibility is the production of an inhibitor which binds to released acetylcholine in the cleft, producing inactivated acetylcholine. Acetylcholinesterase might be more active than normal in the myasthenic patient, producing increased hydrolysis and less available acetylcholine for the receptor site.

The sensitivity of the cholinergic receptor site for cholinergic drugs has been directly measured and is normal. This has been measured by the iontophoresis of acetylcholine as well as the administration of decamethonium or carbachol onto *in vitro* neuromuscular junctions. Thus, from this information the impairment of neuromuscular transmission appears not to be a post-synaptic event but rather a pre-synaptic one.[2]

What is known about the anatomy of the presynaptic nerve terminal in normal and in myasthenic persons, and what is known about the presynaptic events of acetylcholine metabolism in this disease? The vesicle diameter in myasthenic patients is normal, approximately 568 Å. Further, the density of vesicles is normal in this disease. There are about 50 vesicles per square micron in myasthenic persons. The nerve terminal presynaptically is significantly reduced in surface area, however. The average nerve terminal in normal persons is about $3.92 \pm 0.4\ \mu^2$ and in myasthenic persons is about $2.28 \pm 0.2\ \mu^2$, or about 40 percent smaller.[1]

The normal size of the vesicle is one indirect piece of evidence to indicate that the defect is not a disorder in the rate of acetylcholine synthesis. If a motor neuron is stimulated at a high frequency in the presence of hemicholinium to reduce the availability of choline for acetylcholine synthesis, the amplitude of the muscle action potential will fall off rather rapidly, a condition analogous to myasthenia. However, the size of the vesicles is also reduced by about 40 percent in volume and diameter in this experimental situation.[5] The vesicle diameter in myasthenia is normal, however, which is one important bit of information against impaired synthesis. Also, if there were impaired synthesis, one might expect a progressive fall in the amplitude of the miniature end plate potential with repetitive high frequency stimulation. There is in myasthenia, however, a constant reduction in miniature end plate potential amplitude and it does not decrease with further stimulation.[2]

I recently had opportunity to assay the rate of synthesis and rate of hydrolysis of acetylcholine directly by radioisotopic chromatographic assays, utilizing homogenates made from deltoid muscle from normal and myasthenic individuals. The mean specific activity of choline acetylase from 11 controls was 7.6 ± 0.7 nanomoles of acetylcholine formed in 10 minute per mg of protein at 37° C, pH 6.8; and in 10 myasthenic persons it was 5.4 ± 0.7 units, or 30 percent less than in normal controls.[4,5]

I interpret these data as indicating that the defect is not in synthesis of acetylcholine in this disease. I say this for two reasons: (1) there was overlap to a considerable degree in choline acetylase values between normal and myasthenic persons, and (2) there was no correlation in

specific activity in deltoid muscle homogenates from weak and non-weak myasthenic muscle. I think these data reflect the atrophied nerve terminal rather than an impaired rate of synthesis of acetylcholine. The nerve terminal is about 40 percent smaller in myasthenia, and the mean specific activity for choline acetylase was about 30 percent less. Product identification was also carried out by use of labeled choline or labeled acetate, and in both instances the only product produced in the normal and myasthenic homogenate was acetylcholine. This rules out the possibility of a false transmitter which might be a choline analog such as succinylcholine or an acetate analog such as acetylcarnitine. It still leaves open the possibility that there is a noncholine or non-acetate analog which is being synthesized in this disease.

It may be that myasthenia is an autoimmune disease and that the neurophysiological and biochemical changes that I have described may be phenomena secondary to a basic immunological defect.[6,7] Thymic hyperplasia develops in about 80 percent of myasthenic patients, and in about 10 percent a true thymoma develops. Myasthenia develops in about 30 percent of patients who have a thymoma. Furthermore, myasthenia has been associated with other more classically accepted autoimmune diseases such as rheumatoid arthritis, lupus erythematosus, thyroiditis, and polymyositis. Anti-muscle antibodies have been described in about 20 percent of myasthenic patients. Thymectomy may significantly improve a patient or produce a complete remission. A recent study from the Mt. Sinai Hospital in New York indicated that total remission or a significant improvement occurred in 75 percent of myasthenic patients after thymectomy, even if they had the disease more than five years. Many patients had to be followed for some time after thymectomy, sometimes as long as ten to twelve years, before total remission occurred.[8,9] More recently, the use of ACTH and prednisone have been reported to help selected patients significantly. Thymectomy, ACTH and steroids may all be affecting the same immunologic defect at different points.[1] It is possible that there is a clone of B lymphocytes (non-thymus derived) which is producing a toxin or antibody against the neuromuscular junction, resulting in impaired myoneural transmission. One possibility is that this lymphocytic factor is impairing the uptake or release of acetylcholine presynaptically in view of the finding of normal postsynaptic cholinergic sensitivity and normal presynaptic rate of synthesis. The T or thymus derived lymphocyte is known to have a helper effect on increasing the effectiveness of competent immunoglobulin synthesis by the non-thymus derived B lymphocyte. The long time it takes for a response from thymectomy may be the time it takes to dilute out the thymus derived lymphocyte and its known helper effect on stimulating immunoglobulin synthesis by the B lymphocytes.

The management of a myasthenic patient whose condition is deteriorating should include early thymectomy followed by careful titration of anticholinesterase drugs to the maximum therapeutic response. Selected patients may require multiple courses of ACTH to maintain clinical remission, and some patients appear to respond to long-term maintenance with alternate day prednisone. Thymectomy, ACTH, and steroids are effective, as they may directly interfere with the autoimmune process which underlies this disease.

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Refer to: Hypersplenism—Medical Staff Conference, University of California, San Francisco. Calif Med 118:24-29, Jan 1973

MEDICAL STAFF CONFERENCE

Hypersplenism

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* For centuries the spleen has been an enigmatic organ, often the seat of disease but of uncertain function. More recently new insights have been obtained concerning its role in the homeostasis of hemic cells. It has long been said that we shall understand hypersplenism only when we understand "splenism." We have asked Dr. Curt A. Ries, Assistant Clinical Professor of Medicine and Clinical Pathology and Laboratory Medicine, to discuss the pathophysiology of excessive splenic function. A subsidiary and very practical question is: How can we determine when a given patient will benefit from splenectomy? Dr. Ries, please clarify the post-Banti era for us.

DR. RIES:† The association of splenomegaly with reduction of one or more of the circulating blood cells has been known for more than a century. In 1866 Gretsel described the association between splenomegaly and certain types of anemia, which he termed *splenic anemia*.[1] In 1882 Banti published his first description of the association between anemia and splenomegaly, and began a series of experiments demonstrating the pathogenic relationship between the enlarged spleen and the anemia.[2] Banti also described leukopenia in patients with enlarged spleens and noted that frequently these patients died with cirrhosis of the liver. He was the first to question the mechanism of splenic cytopenias, that is, whether the enlarged spleen reduces peripheral blood cell counts by destroying circulating blood cells or by releasing humoral factors which suppress production or release of the blood cells from the bone marrow. Banti also encouraged experimentation with splenectomy in human diseases characterized by splenomegaly and blood cytopenia. Sir Spencer Wells performed the first known therapeutic splenectomy for hemolytic anemia, in 1887.[3] In 1907 Chauffard coined the term hypersplenism, a term which is generally accepted today.[4]

Opinions differ as to what categories of diseases should be included within the definition of hypersplenism. I believe it is useful to define hypersplenism in a functional sense, that is, as those conditions where it is known, either from clinical experience or by kinetic studies using radioactively labeled blood cells, that the spleen is the major site of blood cell destruction and that the peripheral blood cytopenia will be corrected by splenectomy. I define hypersplenism, then, as anemia, leukopenia, thrombocytopenia, or a combination of these resulting from excessive splenic sequestration or pooling of blood cells, usually as-

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†Curt A. Ries, M.D., Assistant Clinical Professor of Medicine, and Clinical Pathology and Laboratory Medicine.

TABLE 1.—*Hypersplenism: Anemia, Leukopenia, Thrombocytopenia, or a Combination of These Resulting from Excessive Splenic Sequestration or Pooling of Blood Cells, Usually Associated with Clinical Splenomegaly and Always Ameliorated by Splenectomy*

—Resulting from splenic enlargement (congestion, infiltration, infection)
—Resulting from intrinsic defects of blood cells (hereditary spherocytosis, sickle cell anemia)
—Resulting from autoimmune destruction of blood cells (autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura)

sociated with clinical splenomegaly and always ameliorated by splenectomy.

Hypersplenism can be divided into three categories (Table 1). The first, hypersplenism resulting from splenic enlargement, is perhaps the most common and best known category. It is the only true hypersplenism—that is, the only instance in which primary changes in the spleen or splenic circulation are solely responsible for excessive destruction of blood cells. Splenic enlargement, when it occurs in the other two categories, is a result of a primary abnormality of the blood cells themselves, or of the interaction of blood cells with humoral factors, leading to abnormal sequestration and destruction of these cells by the spleen. Some investigators do not include these latter two categories within the definition of hypersplenism because the spleen is performing its normal physiologic function, and splenic sequestration is a secondary response to the presence of damaged blood cells in the circulation. I believe it is useful to include these latter two categories, however, since they are cytopenias which in most instances are caused by increased destruction of blood cells in the spleen and are completely ameliorated by the splenectomy.

Ever since the work of Banti in the latter part of the Nineteenth Century, there has been a great deal of interest in the mechanism of hypersplenism. There are at least two possible mechanisms: (a) that the spleen produces humoral factors which suppress production or release of blood cells from the bone marrow, or (b) that the spleen causes cytopenias by excessive pooling, sequestration, or both, and ultimate destruction of the circulating blood cells. Most clinical observations and experimental work support the second hypothesis. There are several lines of evidence for this conclusion. First, the bone marrow of patients with hypersplenism usually shows hyperplasia of the precursors of the cells that are decreased in the peripheral blood. Recent kinetic studies using isotopically labeled blood cells confirm these morphologic observations by demonstrating increased cell destruction with splenic sequestration, and a compensatory increase in production of the involved cell lines by the bone marrow.[5-14] Second, direct counts of blood cells from splenic artery and vein have demonstrated cell density gradients across the splenic circulation in experimental animals and in patients with hypersplenism.[15] Clearly, the reduction in cell density observed in splenic venous blood can be directly attributed to splenic sequestration of these cells. Third, hypersplenism can be induced in experimental animals by various methods, and it can be demonstrated that the resulting cytopenias are caused by splenic sequestration and destruction of the involved blood cells.

Experimentally, one can induce splenomegaly by overloading the reticuloendothelial system by injection of poorly metabolized substances. This can be shown to result in splenic sequestration and destruction of blood cells from all cell lines and in a compensatory increase in production of blood cells by the bone marrow.[16,17] Furthermore, splenic tissue can be implanted into animals that have had splenectomy, and these implants grow and sequester blood cells. Chronic hemolysis produced by acetylphenylhydrazine increases the sequestration of red cells in the splenic implants; the splenic implant enlarges and hypersequestration of all cell lines occurs.[18] If the implant is enclosed within a Millipore diffusion chamber which has been designed to allow passage of humoral factors but not blood cells, sequestration does not occur and cytopenias do not develop.[18] Therefore, it appears from these experiments that the cytopenias develop as a direct result of the destruction of circulating blood cells in the spleen rather than as a result of bone marrow suppression by humoral factors. Because of the many similarities between experimental hypersplenism in animals and hypersplenism in human disease states, it seems quite clear that the primary mechanism causing cytopenias in hypersplenism is increased destruction of blood cells in the spleen.

During the past decade the microscopic anatomy of the spleen has been more clearly defined,

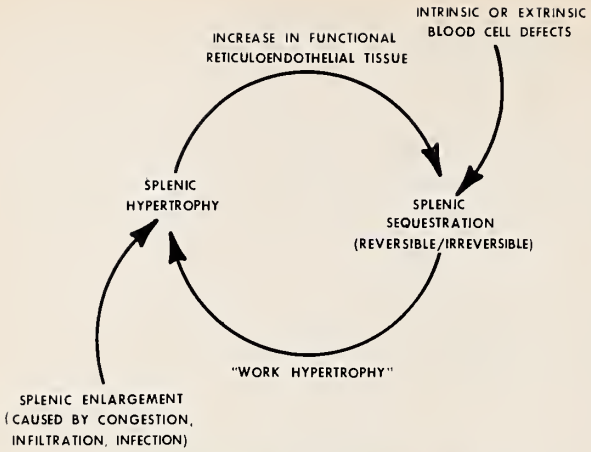


Chart 1.—Pathogenesis of hypersplenism.

resulting in a more precise understanding of the role of the spleen in filtering, remodeling, sequestration and destruction of blood cells.[19-22] The red pulp of the spleen, where these processes occur, is composed of cords and sinuses. The surfaces of these structures are lined by phagocytic macrophages and reticuloendothelial cells. The circulating blood cells enter the splenic cords from the terminal arterioles, pass through fenestrations in the basement membrane between cord and sinus and then through narrow slits between sinus endothelial cells into the sinuses, from which they exit via the splenic veins. The cord-sinus interface provides a unique screen-like filtration system through which all blood cells must pass.[21-22] Openings through the fenestrations and slits measure less than three microns in width, offering a major anatomic barrier to passage of blood cells through the cord-sinus circulation.[21-22] This implies that cell deformability—that is, the ability of blood cells to squeeze through these narrow openings—is essential to prevent abnormal sequestration and destruction of the cells in the spleen. Deformability in turn depends on a healthy, metabolically active blood cell, a pliable and functional membrane, and absence of cytoplasmic inclusions or precipitates which would prevent free flow through the small openings. Abnormal red blood cells, such as those in hereditary spherocytosis, sickle cell anemia, or Heinz body hemolytic anemias, have difficulty passing through these small openings and become trapped in the splenic red pulp.[20] Once sequestered in the spleen, these trapped cells are exposed to metabolic conditions (hypoxia, hypoglycemia, acidosis) which further limit their survival. Ultimately, the cells are destroyed by splenic macrophages and reticuloendothelial cells.

Splenic sequestration may be initiated by either primary splenic enlargement or by intrinsic or extrinsic defects in the blood cells themselves (Chart 1). Regardless of the triggering event, splenic sequestration results in "work hypertrophy" of the spleen, an increase in the functional reticuloendothelial tissue mass, further sequestration, and further splenic hypertrophy.[23] The reversibility of splenic sequestration depends on multiple factors relating to both the spleen and the blood cells themselves. These include size, shape, deformability, and metabolic status of the blood cells; variations in the metabolic environment of the spleen; changes in the size and activity of the splenic phagocytic cell mass; variations in the cord-sinus circulation; and the duration of cell sequestration in the spleen.

Hypersplenism resulting from splenic enlargement has traditionally been considered to be either primary or secondary. It is doubtful, however, whether true primary hypersplenism exists. The older terminologies of primary hypersplenism and primary splenic anemia and neutropenia probably reflect a lack of understanding of the true pathogenesis of these disorders. In the absence of demonstrable histopathologic changes in the spleen and in the absence of portal hypertension, the cytopenias previously regarded as primary hypersplenism are likely the result of either intrinsic defects in the blood cells themselves or immune cytopenias in which antibody activity has not been clearly demonstrated.

The most common causes of hypersplenism resulting from an enlarged spleen are cirrhosis of the liver with portal hypertension and congestive splenomegaly (Banti's syndrome) and neoplastic diseases of the spleen (Table 2). Hypersplenism associated with infection is rare in California, although it is a common problem in tropical countries. The connective tissue diseases and sarcoidosis frequently produce a mild to moderate degree of hypersplenism. In Felty's syndrome severe neutropenia, usually due to hypersplenism, is characteristic.

The use of radioactive labels to determine the survival and sequestration of blood cells has received increasing attention and acceptance since Jandl and associates first described the usefulness of radioactive chromium in the study of

TABLE 2.—*Causes of Hypersplenism Resulting from an Enlarged Spleen*

Congestive splenomegaly	• Cirrhosis of the liver. • External compression or thrombosis of portal or splenic veins.
Neoplastic diseases	• Lymphomas and Hodgkin's disease. • Leukemias (chronic lymphocytic leukemia, chronic myelogenous leukemia, acute leukemias). • Myeloproliferative disorders (polycythemia vera, myelofibrosis with myeloid metaplasia).
Inflammatory diseases	• Acute infections (mononucleosis, hepatitis, subacute bacterial endocarditis). • Chronic infections (tuberculosis, malaria, syphilis, kala-azar). • Sarcoidosis. • Connective tissue diseases (lupus erythematosus, Felty's syndrome).
Reticuloendotheliosis	• Lipoid type (Gaucher's disease, Niemann-Pick disease, Schuller-Christian disease). • Nonlipoid type (Letterer-Siwe disease, acute histiocytoses).

normal and abnormal red blood cell survival and sequestration in man.[5] Similar techniques are now available for the study of platelet survival and sequestration, and a great deal has been learned during the last decade regarding the kinetics of the thrombocytopenias in various clinical disorders.[8-13] Technical difficulties have limited the study of granulocyte kinetics in leukopenic states, and there is still considerable uncertainty as to the underlying defect in many of the syndromes associated with neutropenia.

In hypersplenism resulting from splenic enlargement, such as in congestive splenomegaly, anemia caused by excessive sequestration of red blood cells is usually mild to moderate. However, with massive splenomegaly such as sometimes occurs in the myeloproliferative disorders, lymphoproliferative malignancies, and some of the tropical splenomegalies, a major portion of the total red blood cell pool may be contained within the spleen. Severe anemia may occur in these conditions even when the total body red cell mass is near normal, and splenectomy is frequently of great benefit.[24] By determining blood volume with the "double blood volume" technique (^{51}Cr-red blood cell volume and ^{131}I-albumin plasma volume), together with a ^{51}Cr-red cell survival-sequestration study, one can usually successfully predict whether splenectomy will be helpful. The ^{51}Cr-red cell survival in such cases may be near normal, in spite of the fact that a major portion of the red cell mass is preferentially pooled in the spleen. Patients with myeloid metaplasia may also require ferrokinetic studies to assess the erythropoietic activities in the spleen and bone marrow. Red cell survival and sequestration studies are also indicated in hemolytic anemias associated with splenomegaly and in the auto-immune hemolytic anemias, to determine whether splenectomy will benefit the patient.[6,7] A decidedly shortened ^{51}Cr-red cell survival, associated with progressive accumulation of radioactivity over the spleen, indicates the patient will respond favorably to splenectomy.

During the past few years we have been studying the pathophysiology of thrombocytopenia in various disease states, utilizing the ^{51}Cr-platelet tagging method. Platelets are isolated from one unit of the patient's blood (type specific freshly drawn donor blood is used for isolation of platelets if the patient's platelet count is less than 20,000 per cu mm), labeled with radioactive chromium, washed with autologous plasma, and reinjected into the patient. Blood specimens are taken periodically to establish a platelet survival curve, and surface counts are performed over liver, spleen, and precordium.

In normal volunteers the ^{51}Cr-platelet half-time is approximately four days (Chart 2). Platelet recovery at time zero is 70 percent, as determined by extrapolating the platelet survival curve back to time zero. Thirty percent of platelets are immediately sequestered in the spleen, as reflected by the surface counts. Other investigators report identical findings, and it is our opinion that this 30 percent fraction represents the normal splenic platelet pool.[9-10] After the initial accumulation of splenic radioactivity in normal volunteers, the surface counts over liver and spleen remain more or less stable during the remainder of the platelet survival study.

Representative examples of platelet survival-sequestration studies in patients with acute idiopathic thrombocytopenic purpura (ITP) are

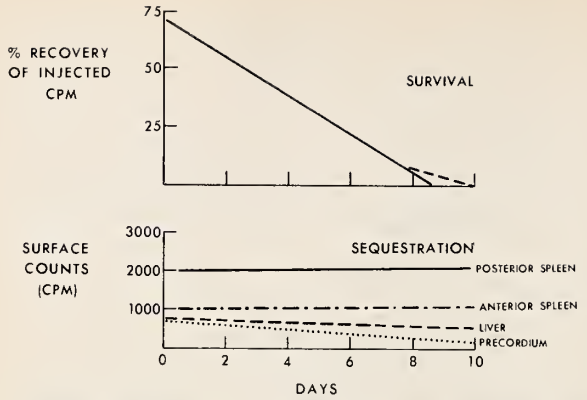


Chart 2.—Study of survival and sequestration of ^{51}Cr-labeled platelets in a normal volunteer. Platelet survival was linear with a $T_{1/2}$ of 4.25 days; platelet recovery at T_0 was 70 percent. Surface counts reflect sequestration of 30 percent of the platelets in the spleen (the normal splenic platelet pool); this "immediate" sequestration occurs within 10 minutes after injection.

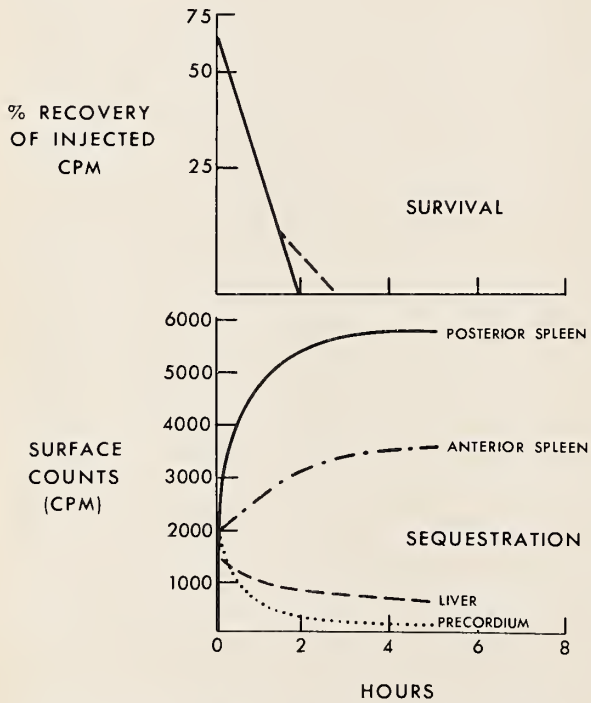


Chart 3.—Platelet survival and sequestration is a patient with acute idiopathic thrombocytopenic purpura and splenic sequestration. Platelet survival was exponential with a $T_{1/2}$ of 1 hour; recovery at T_0 was 70 percent. Surface counts demonstrate progressive splenic sequestration during the platelet survival time. Note that posterior counting over the spleen is much more sensitive than anterior counting for demonstrating splenic sequestration.

shown on Charts 3 and 4. Note that the platelet half-time is extremely short, but the recovery is

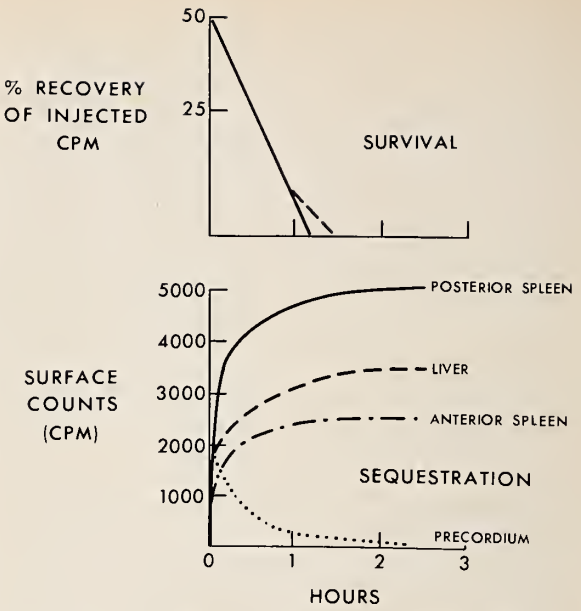


Chart 4.—Platelet survival and sequestration in a patient with acute idiopathic thrombocytopenic purpura and sequestration in both spleen and liver. Platelet survival was exponential with a $T_{1/2}$ of 0.5 hours; recovery at T_0 was 52 percent. Surface counts demonstrate both splenic and hepatic sequestration during the platelet survival time.

essentially normal. The surface counts during the platelet survival time reflect sequestration in the spleen in the first patient, and in both the liver and spleen in the second. The first patient, with splenic sequestration only, had a complete remission after splenectomy, while the second patient, who had both splenic and hepatic sequestration had only partial remission after splenectomy. In our experience with ITP patients, hepatic sequestration does not occur in the absence of splenic sequestration. It is recommended by some investigators that ^{51}Cr-platelet survival-sequestration studies should be done routinely before splenectomy in patients with ITP, in order to predict which ones will have the most successful results.[13] We are accumulating sequestration data on patients with ITP and other forms of thrombocytopenia in an effort to define precise criteria for predicting response to splenectomy.

Patients with thrombocytopenia due to hypersplenism and a markedly enlarged spleen have characteristic platelet kinetics (Chart 5). In contrast to patients with ITP, the abnormality here is one of very low initial platelet recovery. This low recovery is associated with the immediate appearance of very high splenic surface counts,

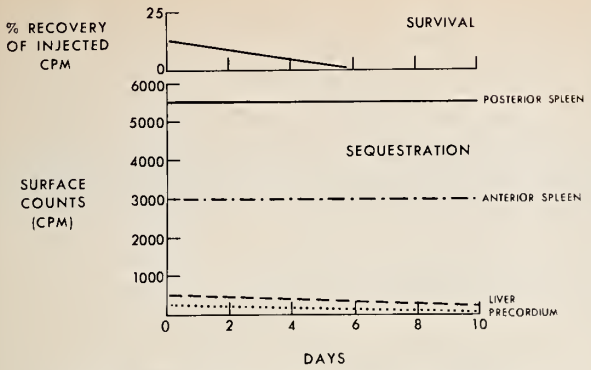


Chart 5.—Platelet survival and sequestration in a patient with hypersplenism caused by congestive splenomegaly (Banti's syndrome). Platelet survival appared to be linear with a $T_{1/2}$ of 3.0 days; platelet recovery at T_0 was 12 percent. The remainder of injected platelets were immediately sequestered in the spleen.

indicating that the normal splenic platelet pool is greatly expanded. In the case illustrated, only 12 percent of the patient's platelets remained in the circulation; the remainder were promptly and preferentially sequestered in the spleen. On the basis of the ^{51}Cr-platelet kinetic data, platelet turnover rates can be calculated to determine whether thrombocytopenia is due to increased destruction, lack of production, or a combination of the two. This kind of information is extremely helpful to the clinician in deciding whether splenectomy should be performed, particularly in patients whose hypersplenism is associated with diseases, such as lymphoma and myelofibrosis that are known to infiltrate the bone marrow.

Technical problems have limited the usefulness of kinetic studies in the evaluation of neutropenic states. Although considerable data have been accumulated on granulocyte kinetics using the DF^{32}p (diisopropyl fluorophosphate) method, this isotope cannot be used for surface counting. While shortened granulocyte survival has been demonstrated in some patients with Felty's syndrome, systemic lupus erythematosus, and cirrhosis associated with splenomegaly, the demonstration of splenic sequestration by radioactivity accumulating over the spleen has not been possible.[14] It seems likely, however, that many patients with these and other diseases do, in fact, have hypersplenism for granulocytes. This is supported by the clinical observations that (a) hyperplasia of the myeloid series is usually present in the bone marrows of these patients, and (b) many of the patients respond to splenectomy.[25] We are hopeful that satisfactory methods for studying granulocyte kinetics, including direct measurement of splenic sequestration, will be available in the near future.

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Important Advances in Clinical Medicine

Epitomes of Progress -- Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance, The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a partciular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Ophthalmology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102.

Hydrophilic "Soft" Contact Lenses

A VARIETY OF "SOFT" CONTACT lenses are under investigation. To date, only the Bausch and Lomb lens has FDA approval, and that only for cosmetic use. None are approved at this time for therapeutic use in ocular diseases. Investigational use of soft lenses in disease states indicates that they will be of significant value in the treatment of dry eye conditions, corneal ulcers, Stevens-Johnson syndrome, ocular pemphigoid, and bullous keratopathy. As there are sharp differences between the various kinds of lenses in composition, tolerance, and absorption and in release of medication, each lens type may find different use indications.

In contrast to hard contact lenses, soft lenses can be comfortably worn over pathologically irregular corneal epithelium, functioning effectively as a patch to reduce eyelid and external irritative factors to allow healing and epithelialization. In bullous keratopathy symptomatic relief is often obtained. No significant improvement in the appearance of the corneal disease is brought about by the lens itself, and consequently no improvement of visual acuity ensues unless used with 5 percent hypertonic saline solution without preservative. In advanced cases removal of the pathologic epithelium and use of cycloplegic agents, antibiotics and hypertonic saline solutions with insertion of the soft lens may give significant improvement.

Preliminary studies on glaucoma patients indicate that the intraocular pressure effect of pilocarpine is greatly enhanced when used with a hydrophilic lens. However, no conventional eye drops can be used with the present soft lens because the concentration of the preservative in the lens destroys the corneal epithelium.

ROBERT V. SHEARER, M.D.

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Blow-out Fractures of the Orbital Floor

FRACTURES OF THE ORBIT AND ORBITAL floor are commonplace, and since 15 to 20 percent of the orbital fractures are associated with serious ocular injuries, ophthalmological consultation is indicated.

Surgical repair of fractures of the floor of the orbit are performed to correct diplopia and to prevent enophthalmos. However, it is felt that this operation should be postponed until the orbital edema and hemorrhages have had time to subside, usually within two weeks. Many of the cases of diplopia do clear up spontaneously and no difference in the prognosis has been demonstrated when operation is delayed that long.

Several cases of visual loss have occurred following orbital floor repair due either to direct trauma to the optic nerve or its blood supply at the time of operation or from compression by a resulting orbital hemorrhage. Operation by a well-trained team that includes an ophthalmologist, and careful daily postoperative examinations, including confrontation fields and ophthalmoscopic study in addition to bedside determination of visual acuity, should keep these serious complications to a minimum.

GEORGE L. TABOR, M.D.

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Management of Congenital Cataracts

EARLY OPERATION FOR bilateral congenital cataracts, whether they are due to rubella, heredity or metabolic disease, is indicated according to most authorities. With the use of contact lenses fitted in the operating room, it is feasible to do a unilateral cataract operation with hope of obtaining some useful vision, although the results so far are not always encouraging.

The reintroduction of the aspiration type of lens extraction in cataracts of infancy and childhood by Scheie, is the generally accepted method today. His principle of using a large-gauge needle is the basis of the operation although there have been many modifications by various surgeons. Long term post-operative use of mydriatics and cycloplegics seems to be imperative.

WARREN A. WILSON, M.D.

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Microsurgery in Open Angle Glaucoma

THE MAIN TREATMENT OF OPEN angle glaucoma is medical, and with the stronger miotics and the carbonic anhydrase inhibitors it was hoped that operation would not be indicated. However, some of the medications were not tolerated or became ineffective, so it is necessary to operate in a number of these cases. The classical antiglaucomatous filtration operations have many complications, the main one being the progression of cataracts.

With the advent of microsurgical techniques, three new methods have been devised:

1. Trabeculotomy, in which a slit is made to open the corneoscleral meshwork and establish a direct communication between Schlemm's canal and anterior chamber.

2. Trabeculectomy, which consists of removing a piece of the corneoscleral meshwork and the underlying Schlemm's canal so there are two openings of the canal in direct communication with the anterior chamber. This procedure has been simplified in Dellaporta's trepanotrabeculectomy.

3. Sinusotomy, or externalization of Schlemm's canal: A strip of sclera overlying Schlemm's canal is removed and a direct communication from the canal to the subconjunctival tissues is created.

The above methods appear to work as well as the classical filteration operations, with fewer complications. However, they can only be performed with the operating microscope.

A. Dellaporta, M.D.

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Strabismus Management

The basic principles of the care of the child with muscle problems remain unchanged. The emphasis is on early detection of strabismus and amblyopia in these children.

Reluctance by the child to have his good eye covered and jerky following movements noted in the poorer eye when the good eye is covered are signs which should alert the pediatrician or the family physician to the possibility of amblyopia. Full-time occlusion of the better eye is still the method of choice to correct amblyopia after determining that there is no other eye disease.

Early operation to correct strabismus is advocated by most ophthalmic physicians, especially in non-accomodative strabismus, which is usually noted shortly after birth. In these cases, glasses do not usually help the deviation and operation is performed between 6 and 18 months of age. Foveal fusion is rarely obtained in congenital esotropia, but peripheral fusion frequently develops following early surgery. In accomodative esotropia with a later onset, glasses, occlusion and orthoptics are used.

The surgical incision of the conjunctiva is now often made near the limbus rather than over the muscle directly. Better functional and cosmetic results have been reported with this incision. Collagen and other new materials are being tried to reduce postoperative suture reactions. The use of thin paste-on Fresnel prisms is now being evaluated to improve fusion where a small postoperative deviation exists.

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Diabetic Retinopathy

Diabetic retinopathy remains a leading cause of blindness in the United States. Approximately 15 percent of the three million diabetics in this country have visual impairment, and it is expected that by the year 2000 there will be 500,000 persons blind because of diabetes.

The more common nonproliferative form, which is characterized by microaneurysms, retinal hemorrhages and exudates, venous abnormalities, and intraretinal shunt vessels, can cause visual loss by macular involvement with edema or exudates or both. The proliferative form of the disease, characterized by new vessel growth on and extending beyond the retinal surface, accompanied by fibrous and glial proliferation, occurs in approximately 6 percent of those with retinopathy and is by far the more destructive form of the disease. Neovascularization and its associated retinal and vitreous hemorrhage, fibrous proliferation, retinal traction, and retinal detachment may lead to blindness in a matter of months in spite of all medical efforts.

Current therapy must include careful regulation of the diabetes from the onset of the disease. Photocoagulation, by ruby and argon laser and xenon arc, permits thermal destruction of vascular abnormalities and may aid in the absorption of intraretinal edema and exudates.

Pituitary ablation is still in use for treatment of severe diabetic retinopathy, but these patients

must fulfill specific criteria. To date, there is no conclusion regarding the value of pituitary ablation.

Despite advances in these techniques, which may permit control of the nonproliferative and proliferative stages of diabetic retinopathy, proper management rests with recognition at the earliest stages of the disease. To improve their visual prognosis, diabetics must have ophthalmic evaluations regularly.

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Rhabdomyosarcoma of the Orbit

ELECTRON MICROSCOPY has become am important method of studying and identifying the different types of orbital tumor.

Rhabdomyosarcoma is the most common malignant tumor of the orbit in children. It may be present at birth but the average age of onset is around 8 years of age. The clinical signs have a rapid evolution with proptosis, lid and conjunctival edema, limitation of motion, papilledema and some pain. Nasal bleeding may occur if the ethmoid area is invaded. The diagnosis is made after biopsy. Histologically the tumors exhibit a varying pattern. It is now believed that, in contrast to those of adults, these tumors do not arise from pre-existing muscles, but originate from undifferentiated orbital mesenchymal tissue. Most rhabdomyosarcomas of the orbit are pleomorphic, exhibiting spindle cells with abundant cytoplasm in some areas, alveolar patterns in others, and differentiation into striated muscle cells in still other portions. Cross striations are found in only 50 to 60 percent of these tumors, and they may be identified in the cells of metastatic lesions in cases where the primary tumor showed no striations. With the electron miscroscope the muscular nature of many of the cells becomes apparent. Some cells show sarcomeres with well developed Z bands, others that are rudimentary. Many cells are encountered in which only bundles of thick and thin actimyosin fibrils are identified.

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Prophylaxis in Cataract Surgery

THE PROLONGED TOPICAL or systemic use of various combinations of antibiotics preoperatively to prevent infection in cataract operations has been discarded and the most recent work by Boyd, Welsh and others indicates that the subconjunctival injection of garamycin (Gentamycin®) 20 mg in solution, upon surgical entry of the operating field, is the best method. This particular antibiotic will penetrate the aqueous humor within five minutes and it is the opinion of the investigators that it is fully five minutes, with the usual preliminaries, before the anterior chamber is actually open.

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Desferrioxamine B in Treatment of Ocular Foreign Bodies

DEFEROXAMINE (DESFERRIOXAMINE B) has been found useful in the treatment of ocular iron-containing foreign bodies which otherwise may produce siderosis bulbi and loss of vision. It has been used for either corneal or intraocular foreign bodies. Skilled surgical extraction is the treatment of choice but if this is unsuccessful deferoxamine therapy should be considered. Five

or ten percent deferoxamine ointment may be applied topically four times daily for a corneal foreign body or rust ring. Also, deferoxamine may be given by subconjunctival injections. For a retained introcular foreign body, 500 mg deferoxamine is given intramuscularly twice daily. The length of treatment may vary widely; sometimes several weeks is needed.

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Ultrasonic Applications in Ocular Trauma

IN TRAUMATIZED EYES, it is difficult to see the anterior segment because of corneal clouding and hyphema. The posterior segment view may be obscured by cataract formation and vitreous hemorrhage. In these circumstances ultrasonography is a valuable mode of investigation of the internal structures of the eye.

The eye is an excellent model for ultrasonic analysis because the reflected echoes from the anterior intraocular structures are separated from the reflections of ultrasound from the posterior wall of the eye by the acoustically empty space of the vitreous.

Instrumentation for "A" mode ultrasonography is becoming more available in local community hospitals. The same basis instrumentation for echoencephalography is used for ophthalmology with a special probe (transducer).

Information can be obtained regarding the presence or absence of suspected intraocular foreign bodies. It is also possible to determine ultrasonographically the magnetic attractiveness of these, which lets the surgeon know before operation whether he is dealing with a magnetic or nonmagnetic foreign body. A change in the echo pattern of the foreign body, if magnetic, is observed during the period the magnet is applied to the globe.

Pathologic conditions of the vitreous such as vitreous hemorrhage and the potential presence of retinal detachment can be determined. There are limitations regarding the extent and reliability of the information gathered ultrasonographically, but it is an innocuous procedure which can provide valuable clinical information.

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Tumor Hypercalcemia

As EARLY AS 1855 CALCIUM abnormalities associated with tumors (ectopic calcification in patients with breast cancer) were described by Virchow.[1,2] In 1899 bone cysts not containing cancer were noted by Stephen Paget in women with breast cancer. This was probably the first suggestion of a humor from a tumor. Hypercalcemia was not associated with breast cancer until 1942. At first it was considered a complication of therapy, but it is now established that hypercalcemia occurs more frequently in the untreated patient and bears no relation to progression or regression of lytic lesions.

In 1961 Warwick et al[3] noted hypercalcemia in 9.1 percent of 438 patients with advanced cancer; however, the increased use of routine chemical screening may well yield a higher incidence today.

The hypercalcemia of malignancy is most commonly associated with osteolytic metastasis. Usually, the serum calcium and phosphate levels are both elevated. A rare cause of hypercalcemia by metastasis is destruction of the adrenal glands, resulting in Addison's disease. The occurrence of hypercalcemia with normal or elevated serum phosphate levels, in patients with or without osseous metastasis has been related to osteolytic compounds present in lipid extracts of tumors and serum. Contained in lipid extracts are phytosteryl esters which have vitamin D-like action on bone. Recently, the osteolytic compound found by Goldhaber in mouse sarcoma has been identified as prostaglandin E_2. Both E_2 and $F_2\propto$ prostaglandins, which have osteolytic activity, also have been found in brochogenic carcinoma, a cancer in which hypercalcemia frequently occurs. They have also been found in human medullary carcinoma of the thyroid where serum calcium levels are normal despite large amounts of calcitonin.

In a third variety of hypercalcemia, hypophosphatemia and low tubular reabsorption of phosphate (TRP) are present. This is now known to result from the elaboration of parathyroid-like hormone(s) by non-parathyroid cancers. This syndrome was postulated by Fuller Albright in 1941 because the *low* serum phosphate level could not be explained by excessive breakdown of bone. Twenty-five years later, his hypothesis was confirmed by direct immunoassays of parathyroid hormone (PTH) in malignant tissues and in blood. The laboratories of Tashjian et al, Sherwood et al, and Berson and Yalow, and our own laboratory, have confirmed the production of parathyroid-like hormone(s) by cancers of lung, kidney, colon, ovary and cervix. Berson and Yalow, and we too, have extended Albright's observation to show that PTH is increased in the serum of many patients with cancer but without hypercalcemia.[1,2]

Clinically, the hypercalcemia which results from the direct invasion of bone or from humoral processes may be compounded and exaggerated by immobilization, by dehydration, and by thiazide therapy. Prophylactic hydration and ambulation have proved effective in reducing the frequency of hypercalcemia in cancer patients.

The less common variety of hypercalcemia in which PTH is elaborated by malignant neoplasms is signaled by a low serum phosphate level and a low TRP. Caution must be observed in interpreting phosphate abnormalities in patients receiving glucose infusions or corticoids, either of which lowers the serum phosphate level. Thus hypophosphatemia in a hypercalcemic patient receiving glucose or corticoids does not necessarily indicate that the hypercalcemia is due to hyperparathyroidism.

Direct measurement of PTH is of help. Using both a chicken antiserum and a guinea pig antiserum developed against bovine PTH in a radioimmunoassay, we found identical reactivities of these antisera to the peptides extracted from the

parathyroid glands or in sera from patients with either primary hyperparathyroidism or the secondary hyperparathyroidism of uremia. They also react equally to the synthetic amino terminal 1-34 amino acid peptide (the biologically active sequence). In the sera of 11 patients with hypercalcemia and malignant disease *other than breast carcinoma*, the guinea pig antiserum detected immunoreactive PTH which the chicken antiserum did not. In three other sera, the chicken antiserum recognized material which the guinea pig did not. In none of the sera from patients with malignant disease and hypercalcemia did the two antisera detect immunoreactive PTH equally.[1,2] This shows that the ectopically produced PTH is immunologically different from that of the normal, adenomatous or hyperplastic parathyroid gland. Riggs et al[4] confirmed and extended this observation and reported the radioimmunoassay helpful in differentiating primary from ectopic hyperparathyroidism.

Establishing the cause of hypercalcemia in a patient with cancer poses a particular problem. Hypercalcemia may arise from the cancer by one of the mechanisms listed above, or it may arise co-incidentally—for example, from a parathyroid adenoma. It is, therefore, important to know that certain cancers are not associated with ectopic elaboration of parathyroid hormone. Of these, the most important is breast cancer, for these reasons: 85 percent of patients who have it ultimately show osseous metastasis, it is the cancer most commonly associated with hypercalcemia and it does *not* elaborate PTH. The hypercalcemia of breast cancer is usually but not always associated with osteolytic metastasis and in our experience is not associated with a low serum phosphate level or low TRP unless artifactually induced by glucose or corticoid administration. Thus the presence of hypercalcemia, hypophosphatemia and low TRP in a patient with breast cancer indicates an additional diagnosis. The diagnosis of co-incidental parathyroid adenoma in disseminated breast cancer has been verified to our knowledge in 16 patients. This association should be borne in mind, since neither breast cancer nor hyperparathyroidism is a rare condition and the combination is statistically far from unlikely.

The prognosis of hypercalcemia depends on the intensity of the process, the speed with which it is recognized, and the vigor with which it is treated. Most hypercalcemias of cancer respond well to relatively simple measures, such as hydration or corticoids. In patients who respond to treatment, the prognosis is that of the underlying disease, rather than of the hypercalcemia. Thus some women with indolent metastatic breast cancer may live comfortably for years if their hypercalcemia is corrected.

The report (printed elsewhere in this issue of CALIFORNIA MEDICINE) of two cases of hepatoma with hypercalcemia and hypophosphatemia illustrates several points. First, hypercalcemia of considerable degree may be present without lethargy. Weight loss may occur in patients with primary hyperparathyroidism due to anorexia, but losses in weight greater than ten pounds are more frequent with cancers. The need to consider hypercalcemia in each patient with malignant disease is emphasized.

Although hepatoma is an infrequent cause of death (three of every thousand autopsies) and hypercalcemia has not been a prominent part of its clinical picture, the increasing number of reports of ectopic production of parathyroid hormone by hepatomas suggests that this possibility should be considered in each patient with hepatoma. Direct measurement of PTH has been made in only one case,[5] but other clear-cut instances of ectopic production of PTH by hepatomas have been recorded as reported and reviewed in this issue. Presence of phytosterols in animal hepatomas has been noted, but the potent osteolytic short-chain esters of stigmasterol and Δ-7 sitosterol were not specifically looked for, nor have prostaglandins or other osteolytic humors been sought. It is clear that almost all malignant lesions can affect the host by elaboration of many humors. Knowledge of the pathophysiology of the hypercalcemia or malignant disease is progressing rapidly. Patient care can only benefit.

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Myasthenia Gravis After 300 Years: Continued Search

In 1972 we marked the tricentennial description by Thomas Willis of what we now call myasthenia gravis. Willis, a physician, anatomist, and early biochemist, suggests, "Sometimes the imbecility and impotency of local motion doth in some measure also depend upon the fault of the explosive Copula, suffused everywhere from the blood into the moving Fibres."[1] It was over two and a half centuries later that Loewi and Dale showed that acetylcholine was the chemical transmitter of the nerve impulse and that cholinesterase stopped the activity of acetylcholine.[2,3] Much additional information has been learned about neuromuscular transmission. This is very well summarized by Drs. Rosenberg and Campbell in the Specialty Conference which appears elsewhere in this issue. But the application of this information to the clinical problems found in myasthenia gravis leaves many questions unanswered. Myasthenia gravis has no respect for youth or age. It may be recurrent and relentless in its course in spite of anticholinesterase treatment, thymectomy, mechanical respiratory support, and resuscitative measures, as it was in the seven-year-old patient who was presented in the Specialty Conference. There is a demonstrable defect in neuromuscular transmission, which is improved incompletely by anticholinesterase treatment. Evaluation of the block and effectiveness of treatment by day-to-day repetitive nerve muscle stimulation at 3 to 20 electrical shocks per second is a test not likely to be accepted or tolerated by many patients. Slomic et al and Özdemir and Young have pointed out the applicability and limitations of these techniques for diagnosis and evaluation of myasthenic patients.[4,5] The latter investigators report inability to demonstrate decrement in 13 percent of their patients even when testing three muscles in each case. There is some variation in administration and dosage of the edrophonium (Tensilon) test by physicians. However, the dosage of 10 to 15 mg of edrophonium injected intravenously over a 90-second period as outlined by Rosenberg and Campbell is higher for adults than the 2 mg and 8 mg doses at 45-second intervals recommended for most adults based on 25,000 tests by Osserman et al, who originated the test.[6] Their recommended intravenous dosage for children is 0.5 mg for infants, 1 mg for children weighing up to 75 pounds, and 2 mg for those above that weight.

In the child presented in the Specialty Conference the thymus was described as "entirely normal," not having the lymphoid germinal centers or "hyperplasia" so often found at thymectomy or autopsy. Thymoma would be, admittedly, unlikely in a child of seven with myasthenia since it is seldom seen in myasthenia beginning before the age of 20 or after the age of 70.[7] However, the autopsy showed lymphorrhages in both cardiac and striated muscle. That the heart muscle may be involved in this way has been recognized by Genkins et al and by others.[8] The presence of these lymphoid elements has been used to support the concept of an autoimmune disorder with possible cellular hypersensitivity as playing some etiologic part.[9] Earlier demonstrations of a circulating antibody to striated skeletal and cardiac muscle and myoid cells of the thymus in less than a third of all myasthenic patients has not explained the defect of neuromuscular transmission in myasthenia gravis.[10,11,12] Goldstein and Manganaro's proposal, from experimental animal studies, that the thymus develops an autoimmune thymitis and elaborates a substance, "thymin," as a consequence of this, causing the neuromuscular block in myasthenia, is intriguing. But much remains to be reconciled with this postulation.[13]

Engel and Santa have shown by electronmicroscopy that there are structural alterations in the neuromuscular junction in the nerve terminal and postsynaptic membrane of intercostal muscle in myasthenia gravis as compared with the normal.[14] However, subsequent studies by them, using rats treated with anticholinesterase drugs compared with untreated controls, showed that the treated animals had structural changes quite similar to those seen previously in the human neuromuscular junctions of patients, the majority of whom

had been treated with similar drugs.[15] This raises the serious question of whether the structural alterations may not be, at least in part, drug-induced. Clinically we have noted that patients receiving increasing amounts of anticholinesterase drugs may become insensitive, resistant, or unresponsive after a time, showing mainly muscarinic side effects from the medication, then increasing weakness. On withdrawal of these drugs they become still weaker for several days; then, in another several days, strength improves while they still are not receiving the drug, finally surpassing the strength before the drug was stopped. This suggests that prolonged and high-dose anticholinesterase treatment may have an adverse effect on neuromuscular junctions and that if it is withdrawn and the patient supported by other mechanical means for a time the junctions may in part reconstitute themselves.[16,17] It should be remembered that anticholinesterase compounds used to treat myasthenia gravis are not naturally-occurring substances in the body and, hence, not something lacking and to be replaced. Therapeutic enthusiasm by patient and physician alike for these agents should be tempered with caution, since they are pharmacological two-edged swords and not the solution to myasthenia gravis.

The reintroduction of high-dose ACTH treatment of severe myasthenia gravis by von Reis et al, with the aid of tracheostomy and mechanical respiratory support, proved beneficial to many patients with generalized myasthenia who responded poorly to anticholinesterase medication.[18] More recently, the introduction of alternate-day, high-dose prednisone treatment of myasthenia gravis by Engel and Warmolts to support their concept of impaired excitatory factor in this disorder has met with encouraging success.[19] The long-term results and side effects remain to be evaluated. The underlying mechanisms such as alterations of immunological reactions and membrane stability by which improvement is achieved can only be speculated upon at this time.

At this tricentennial of the description of myasthenia gravis we should pause to reflect, take stock, and inquire. Is myasthenia gravis a single disorder from the etiological standpoint? Or, is it an etiologically heterogeneous group of disorders affecting neuromuscular transmission presenting similar but variable features and manifestations which, through ignorance and for convenience, we have lumped together clinically into what we term myasthenia gravis? Is it a single disorder etiologically with variable clinical manifestations and severity? What role, if any, do the various immunological abnormalities play in the cause, or are they simply epiphenomena deriving from as yet undetected virus, toxin, bacteria, or other agent acting upon or in combination with other parts of the body such as the thymus or lymphoreticuloendothelial system to produce defective neuromuscular transmission in some way? What determines which neuromuscular junctions shall be affected or shall lack excitatory transmitter, resulting in weakness? Is the basic defect further up the line, perhaps in the cell body of the neuron? Is it defective in production of axoplasm or precursors of acetylcholine? If there is a circulating substance adversely affecting neuromuscular transmission, why are not all junctions equally affected? What passes from some myasthenic mothers to certain of their infants to cause the transient neonatal myasthenia in the infant? What determines spontaneous remission in a few patients? These are only a few unanswered, perplexing questions. The cause and cure of what we clinically call myasthenia gravis remains obscure. Many bits of this tantalizing clinical puzzle are known, but much remains to be learned and put into place to solve the rest. With greater interest, new and improved techniques for study of neuromuscular function, we may hope to achieve some solution soon.

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Professional Standards Review Organizations (PSRO's)

H.R. 1, THE SOCIAL SECURITY amendment bill, was passed by the House and Senate on October 17, 1972, and signed by the President on October 30. It is now known as Public Law 92-603. It is profoundly complex and there are some who doubt that it can ever be administered at all. Section 249F requires that Professional Standards Review Organizations (PSRO) be set up "in order to promote the effective, efficient and economical delivery of health care services of proper quality for which payment can be made, in whole or in part, under the Social Security Act . . ."

The decision has now been made. Unless the PSRO provisions of the law are repealed or substantially changed, the Federal Government has for practical purposes assumed responsibility for professional standards review for health care services. The law went into effect January 1, 1973. By January 1974 the Secretary of Health, Education and Welfare must have designated the PSRO areas, and as soon thereafter as possible he must designate the PSRO for each area. PSRO's will collect data, information and records as directed by the HEW Secretary who will have access to them. PSRO's must use only M.D.'s and D.O.'s to review actions of their peers. Until January 1, 1976, physician organizations have priority in establishing PSRO's. After that the Secretary can designate a "qualified" public or non-profit organization to serve as the PSRO. The expenses of PRSO's are to be underwritten by the Department of Health, Education and Welfare.

The initial thrust is for utilization control for health care services paid for under the Social Security Act, and specifically for review of institutional care and services. When this legislation was under consideration by the Congress, the American Medical Association and the California Medical Association questioned whether a government operated program of mandatory peer review geared in large part to cost control could be effective without reducing the quality of patient care. This now remains to be seen. And there are certain to be difficulties in establishing the professional standards without compromising the quality of care rendered, particularly to those who deviate significantly from the statistical or standard norms, unless the strengths of the present system which permits peer review of the particular circumstances of a given case can somehow be preserved.

One may anticipate that the most difficult problems will arise around the funding of PSRO's by HEW. It is well known that when the government pays the piper it can call the tune. There are obvious dangers here. But perhaps even more important are the dangers of underfunding of PSRO's by government. It seems inevitable that this will occur sooner or later, and when it does it will be difficult to prevent the program from failing, and when this occurs the way will be opened for other and perhaps non-professional control of quality and costs in health care.

The medical profession has no alternative but to try to make PSRO work, and this is likely to be difficult to do.

—MSMW

Weinberger to HEW

We applaud the selection of Casper W. "Cap" Weinberger to be Secretary of Health, Education and Welfare. He is well known in California for his intellect, erudition and integrity and for his very considerable administrative and fiscal skills. He is also known for his interest in people and his broad knowledge of social problems.

Health, education and welfare (particularly if this is used in the broad sense of well-being) are what it is all about as far as human life and living are concerned. They make possible the pursuit of personal happiness. They are also of growing national concern, and as everyone knows the Federal Government has become increasingly involved through the Department of Health, Education and Welfare (DHEW) until now it controls a very substantial portion of all the funds expended in these fields. Since our government by law must direct and control all expenditures of public funds DHEW is destined to touch the lives of all Americans. Indeed, it has already begun to do so.

It is necessary and proper to spend money for health, education and welfare but so far the government's track record has not always been good. Some of the purposes for which funding has been offered have not been the right purposes. All too often federal funding policies change without preparation or warning and programs well on their way to being useful and productive are suddenly diverted or dismantled, with enormous waste of human effort and money resulting. And there is much experience to show that attempts to control costs by rigid regulation and so-called cost controls restrict the freedom of action which is necessary for human well-being and have almost always either added to the costs or reduced what can be accomplished with the same amount of money. A basic reason for all of this seems to be that the planning, programming, and control have not been where the action is, *i.e.* where the health needs are, where the educational needs are and where the welfare needs are. Nor have the people who are expected to carry out the plans or programs so far had much if anything to say about their development; consequently they have had little interest in their success or failure.

We have great hopes and expectations of the new Secretary. We have been told that he is expected to reduce the number of dollars spent by DHEW, and this need not be bad. We hope and expect that he will recognize the very real dependence upon the Federal Government which has come about in health, education and welfare in this country. And we hope and expect that he will achieve his greatest success by making those DHEW dollars which are spent, far more useful and effective than has so often been the case to date, particularly in health, which is the field we know best. We hope and expect that under his leadership we will begin to get a dollar's worth of health, education and well-being for each dollar spent. When this has been achieved, cutting back on the number of dollars spent will seem less important.

"Cap," we wish you well.

—MSMW

LETTERS *to the Editor*

The Meaning of *Dysmature*

To the Editor: I should like to question Dr. Gluck's use of the term *dysmature* to describe all babies "who at birth are small for their length of gestation."[1] Classically this term has been used to describe babies who are long and thin at birth.[2,3] The implication being that these babies are born malnourished secondary to placental dysfunction.

Many descriptive phrases have been coined to describe the baby who is both light of weight and short in length at birth, *e. g.* pseudoprematurity,[4] intrauterine growth retardation,[5] low-birth-weight dwarfism,[6] small-for-dates, and small-for-gestational age.[7] To widen the concept of the word *dysmature* to include infants affected by a variety of genetic and chromosomal diseases, multiple malformation syndromes and intrauterine infections would, it seems to me, only lead to further confusion.

The confusion already present in the literature is aptly shown by a recent article[8] which proposed to demonstrate fetal asphyxia in infants with intrauterine growth retardation. Actually what the authors described was fetal distress in dysmature babies,[9] a finding published at least 14 years previously.[2]

GLENN SZALAY, M.D.
Harbor City

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The CALPAC Record

To the Editor: As Chairman of the California Medical Political Action Committee (CALPAC) I would like to salute you for your very excellent and perceptive editorial (AMPAC-CALPAC) in the November issue of California Medicine.

Now that the November election results are known, I would like to report to you on our record of success. Totally, we contributed to 130 candidates running for state and federal office in California. Fifty-seven percent of them were Republicans and 43% were Democrats. Three of these candidates were defeated in the June primary and two were not up for re-election until 1974. Of the remaining 125 who appeared on the November ballot, 108 were elected to office. Our success record of 86% is unsurpassed in light of the extent of our political action activity.

As you stated "political committees are important, but alone they are not enough, and this truth should never be forgotten." Our hope, of course, is that medicine will take advantage of the opportunity that this political action affords and have in-put with those legislators on issues affecting the practice of medicine and our patients.

AMPAC and CALPAC's goal through political action is to establish a climate for improved com-

munication with our California lawmakers. Now it is incumbent upon physicians to use this entree to effectively present our case, intelligently explore our positions and seek their support or opposition on legislative proposals as they may or may not be in our best interests or our patients'.

Whether AMPAC-CALPAC's success can be transplanted to future legislative victories is the real test of our effectiveness. Only through continuing membership support can AMPAC-CALPAC be prepared to play an even more vital role in the 1974 elections, and only through physicians at the local level communicating with their legislators can the value of our political action be accurately appraised.

Sincerely,

JAMES C. MACLAGGAN, M.D.
Chairman
CALPAC Board of Directors

Multiple Prescription Blanks

To the Editor: I am replying to the letter written by Mr. Levine in your November 1972 issue.

Our office (four pediatricians) recently purchased a trial supply of multiple prescription blanks. Based on my initial experience with them, I must disagree with Mr. Levine. I like the system and so do our local pharmacists, so they've told me.

On the reverse side of the blank is a specifically designed space for just the information Mr. Levine stipulates the druggist will affix to the prescription and there is plenty of room for this purpose. Using the multiple prescription blanks there is less chance that the patient will lose a prescription or withhold one for a future date (in my experience a rather common problem).

As to the argument that mistakes may be made; well, any prescription is only as good as the pharmacist who fills it. And certainly accuracy is not too much to ask. This is more than amply rewarded by reduced filing space and more accurate and available prescription filing made possible by fewer prescriptions per patient. And lastly it frankly reduces the redundancy of names, addresses, etc. that I have to write and allows me to spend more time on patient care.

In conclusion I think I'll keep my multiple prescription blanks.

MYRON M. FABER, M.D.
San Francisco

Of Drugs and Races

To the Editor: There is apparently a large reservoir of strong opinion among diverse groups that many bad decisions were made at the recent Olympic Games in Germany. Among the most flagrant was the disqualification of Rick DeMont in the 400 meter swimming freestyle event for alleged violation of the rule against taking "pep pills," the loss of his gold medal and the later barring of his participation in the 1500 meter freestyle.

I have received a letter from Mr. Albert Schoenfield, editor and publisher of *Swimming World* magazine, informing me that a group is actively pursuing this matter with the object of persuading the U.S. Olympic Committee to appeal this before the International Olympic Committee when they will hear such matters in February.

May I take this opportunity to appeal through the pages of CALIFORNIA MEDICINE to readers who feel that the DeMont case was unjustly handled to indicate their concurrence by dropping a post card to CALIFORNIA MEDICINE. Since the circumstances leading up to the disciplinary action involve medical considerations to such a degree, it would be especially helpful, I think, to have a strong voice of protest from physicians.

THAYER A. SMITH, M.D.
Norwalk

CASE REPORTS

Refer to: Cohn LH, Hultgren HN, Angell WW, et al: Prolapsing mitral valve with mucinous degeneration—A possible relation to the syndrome of midsystolic click and late systolic murmur. Calif Med 118:43-47, Jan 1973

Prolapsing Mitral Valve With Mucinous Degeneration

A Possible Relation to the Syndrome of Midsystolic Click and Late Systolic Murmur

LAWRENCE H. COHN, M.D.,
HERBERT N. HULTGREN, M.D.,
WILLIAM W. ANGELL, M.D.,
TODD M. GREHL, M.D., AND
JON C. KOSEK, M.D., *Stanford*

THE BILLOWING POSTERIOR LEAFLET of the mitral valve which is associated with the midsystolic click and late systolic murmur is an unusual cause of severe mitral regurgitation, and therefore rarely requires surgical intervention.[1-13] Operation may be necessary in cases in which mitral regurgitation has been worsened by bacterial endocarditis, which is now a recognized complication of this syndrome.

It is the purpose of this report to describe a patient with the billowing posterior leaflet syndrome who required valve replacement for severe mitral regurgitation following two previous episodes of bacterial endocarditis. Histologic studies of the excised valve revealed pronounced mucinous degeneration of the leaflet and adjacent chordae without evidence of previous endocarditis, suggesting that mucinous degeneration was the basis for progressive mitral regurgitation.

Immediately following operation, evidence of transient ischemic myocardial injury appeared in the electrocardiogram in leads 2-3 and AVF associated with a rise in serum enzymes. There was no evidence of coronary artery stenosis. The mechanism of T wave inversion in leads reflecting the diaphragmatic portion of the left ventricular myocardium in patients with the billowing posterior leaflet syndrome appeared related to the abnormal posterior leaflet, since T wave inversion disappeared following valve replacement.

Report of a Case

A heart murmur had been first noted in the patient, a man now 48 years of age, upon discharge from the Army 25 years previously. Two years later in a routine physical examination his physician noted a prominent apical midsystolic click, followed by a grade 3/6 systolic murmur. There was no history of rheumatic fever. Ten years before the present admission bacterial endocarditis developed, manifested by fatigue, fever, splenomegaly, petechiae and increased intensity of the apical murmur. He was treated with penicillin intravenously for six weeks. Four years before admission endocarditis again developed due to an alpha hemolytic streptococcus. Intravenous penicillin was administered again for two months, with recovery. In the year preceding admission, increasingly severe exertional dyspnea and fatigue kept the patient from working as an owner of a trucking company. He was considered a functional Class III patient (New York Heart Association definition).

On physical examination the patient was moderately dyspneic and the blood pressure was 130/80 mm of mercury. A moderate left ventricular heave was palpable 2 cm lateral to the midclavicular line. A grade 4/6 systolic murmur

From The Cardiology Service, Veterans Administration Hosiptal, Palo Alto.

Submitted April 17, 1972.

Reprint requests to: H. N. Hultgren, M.D., Cardiology Service, Veterans Administration Hospital, 3801 Miranda Avenue, Palo Alto, Ca. 94304.

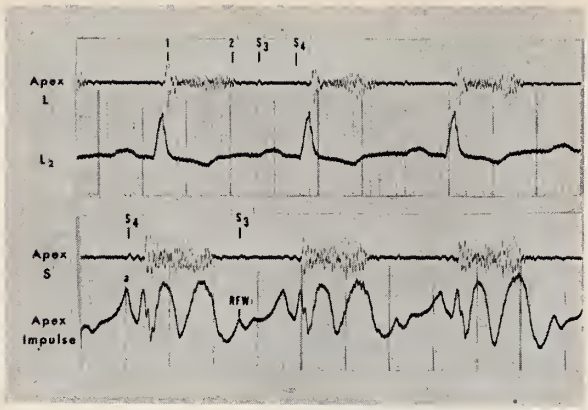


Figure 1.—Preoperative phonocardiogram. Note systolic murmur with late systolic accentuation and 4th and 3rd sound gallops.

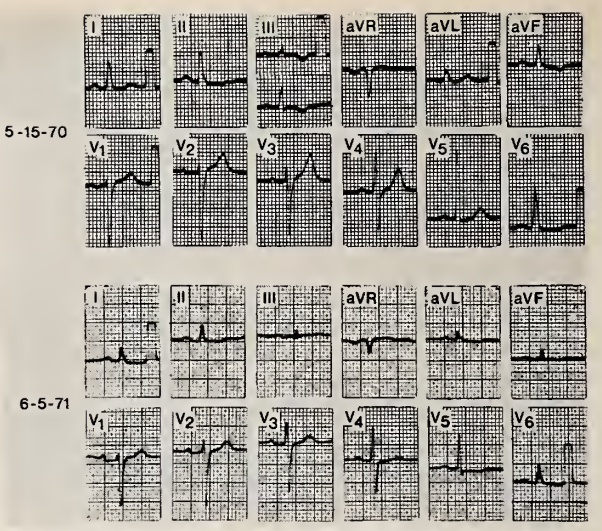


Figure 2.—*Top*, preoperative electrocardiogram. Note T wave inversions in leads 2-3 and aVF. *Bottom*, electrocardiogram recorded 11 months after operation. T wave inversion is no longer present in inferior leads.

was present at the apex and transmitted to the axilla and to the upper left sternal edge. No click was noted. A palpable thrill was present. The murmur was accentuated in late systole. A third heart sound but no diastolic murmur was noted. No other murmurs were present and second sound splitting was normal. The jugular pulse was normal and the arterial pulses were of normal volume but quickly rising. A phonocardiogram confirmed the ascultatory findings (Figure 1). An electrocardiogram demonstrated abnormal P waves suggesting left atrial enlargement and late T wave inversion in leads 2-3 and AVF (Figure 2). Roentgenograms of the chest revealed moderate enlargement of the left ventricle and left atrium with moderate pulmonary congestion. No calcium was seen in the region of the mitral valve by fluoroscopy using an image intensifier.

Cardiac catheterization revealed the following pertinent values:

	Pressures	
RA Mean	8 mm	BA 115/70
PA S/D	30/16	
PA mean	22	
PA wedge mean	13	

The A-V oxygen difference was 5.1 ml/100 ml; the cardiac index was 3.0 liters per minute per square meter. A prominent v wave was present in the pulmonary artery wedge pressure tracing (peak v wave pressure 17 mm). Infusion of methoxamine and supine exercise increased the height of the v wave to 44 and 40 mm respectively. Left ventricular angiography revealed 3+ (0-4) mitral regurgitation with prolapse of the

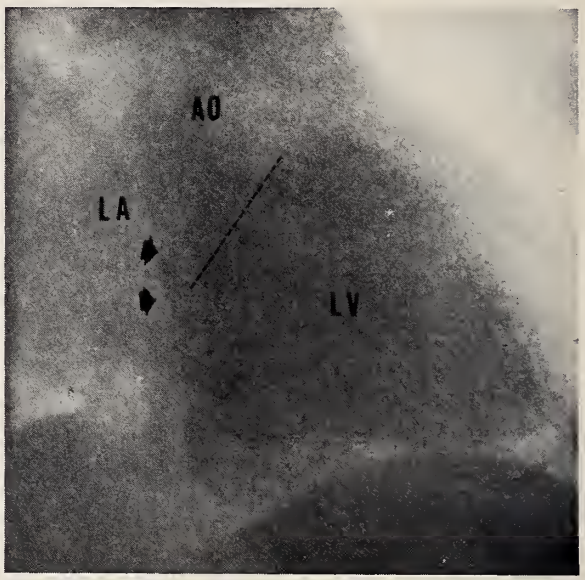


Figure 3.—Left ventricular angiogram showing billowing of posterior leaflet during ventricular systole. The dashed line indicates the position of the mitral orifice. Arrows show prolapsing mitral leaflet.

posterior mitral leaflet characteristic of billowing posterior leaflet syndrome (Figure 3). No aortic regurgitation was present. Ventricular contractility was normal. The ejection fraction was 68 percent. Coronary arteriography was not performed.

Operation was carried out on May 18, 1970. The left atrium was tense and dilated and no



Figure 4.—*Top*, prolapsed posterior mitral valve leaflet during operation, viewed through atriotomy. *Below*, same view with curved clamp elevating the leaflet.

diastolic pressure gradient was recorded between the left atrium and left ventricle. The central portion of the posterior leaflet of the mitral valve was redundant and ballooned into the atrium. The chordae were decidedly elongated and thickened. The papillary muscles and the anterior mitral leaflet were normal. The aortic valve, coronary arteries and left ventricular myocardium were normal to palpation and inspection. There was no evidence of healed endocarditis on either the mitral or the aortic valve. No ruptured chordae were noted (Figures 4 and 5). The mitral valve was excised and replaced with a fresh, aortic homograft mounted on a 28 mm I.D. Shumway-Angell-Cutter support ring. Histologic study of the mitral valve revealed fibroblast proliferation and thickening of the cusps to as much as 4 mm by extensive deposition of acidic (basophilic) stromal mucin. No inflammatory changes were noted, and the valve was avascular (Figure 6). The adjacent papillary muscles were normal.



Figure 5.—Excised mitral valve.

Postoperatively evidence of ischemic myocardial injury appeared on the first day and subsided over the next six days. ST elevations were prominent in leads 2, 3 AVF and V_{5-6}. The ST segments in AVL were not elevated. QRS changes were not observed. Serum SGOT and LDH levels rose to 269 and 1780 units respectively during the first three postoperative days. Atrial arrhythmias consisting of atrial premature beats and transient atrial flutter with 2:1 AV block appeared during the second week after operation. The rhythm was controlled by digitalis and propanolol, and sinus rhythm spontaneously resumed on the 12th postoperative day. The patient was discharged on the 15th postoperative day.

At last report the patient was working full-time without symptoms. An electrocardiogram 11 months after operation showed only minor T wave abnormalities. The deep T wave inversion in the inferior leads was no longer present (Figure 2).

Discussion

The clinical and angiographic features of the billowing posterior mitral leaflet syndrome have been defined by many investigators.[1-9] In most cases the degree of mitral regurgitation is not severe enough to warrant operation. However, endocarditis although it is a rare complication may so greatly increase regurgitation that surgical correction is necessary.[5,10-13]

The patient described in the present study clearly had a midsystolic click and a late systolic murmur for ten years without symptoms. The click and murmur were noted by several physicians. Following two episodes of bacterial en-



Figure 6.—*Left*, two cross-sections of resected mitral valve leaflets. Note thickening by fibrosis and by central dark (basophilic) mucinous degeneration. Tips of leaflets are at top. Hemotoxylin and eosin stain, x 10. *Right*, insert from Figure 4, from junction of dark (basophilic) mucinous zone (below) with lighter (eosinophilic) fibrous tissue (above). Hemotoxylin and eosin stain, x 600.

docarditis, the systolic murmur became louder, filling the systole so that the midsystolic click was not heard. At operation no valve scars were observed, and there was no evidence of chordal rupture to account for the change in the murmur. It is possible that chordal scarring not evident in the excised valve may have permitted more mitral regurgitation to occur. An alternate explanation for the increase in the degree of mitral regurgitation is progressive mucinous degeneration of the valve leaflets and chordae. Mucinous degeneration of the mitral valve has been reported in Marfan's syndrome,[17,19,20] the floppy mitral valve syndrome[15,16,18] and in the billowing posterior mitral leaflet syndrome.[6,9] The "floppy valve" syndrome described by Reid[15] is probably not a true form of the billowing posterior leaflet syndrome since the auscultatory and angiographic features are not present. Three patients with the billowing posterior leaflet syndrome who required valve replacement have been reported by Bittar and Sosa.[9] These patients had mucinous degeneration of the valve. Observations at operation revealed large mitral leaflets which prolapsed into the left atrium during ventricular systole. Preoperative data, however, do not clearly indicate that these patients had a midsystolic click or late systolic murmur.

A frequent electrocardiographic finding in patients with prolapsing mitral leaflet syndrome is inversion of T waves in leads 2-3 and AVF and ventricular premature beats.[3,7,14] Exercise may be accompanied by the appearance of ventricular premature beats, and it has been suggested that occasional instances of sudden death in this syndrome may be due to ventricular fibrillation.[21]

The mechanism of the electrocardiogram changes is not known but the T wave changes suggest ischemia of the posterior-inferior area of the left ventricle. Barlow suggested that distortion of the circumflex branch of the left coronary artery by the prolapsed posterior mitral valve

leaflet may impair blood flow to this area of myocardium by occlusion or thrombosis.[3] Trent observed abnormal amounts of fibrosis in the left ventricular wall at the base of the posterior papillary muscle extending into the muscle itself.[22] Grossman demonstrated angiographic abnormalities of contraction in this area of the myocardium.[23]

The data in this report support the view that blood flow to the posterior-inferior area of the left ventricle is impaired. If the impairment of blood flow were due to the prolapse of the posterior valve leaflet alone, this should be corrected by valve replacement. This was observed in the patient in the present study. Abnormal T waves in leads 2-3 and AVF still were no longer present when the patient was examined six months after valve replacement. The occurrence of acute ischemic changes in the electrocardiogram following operation, associated with an abnormal serum enzyme rise, suggests that during cardiopulmonary by-pass inadequate oxygenation of the posterior-inferior left ventricular myocardium occurred. Aortic cross clamp time, total perfusion time and the total duration of operation were not unduly prolonged. There was no evidence of coronary air embolism. Previous studies of ischemic injury and myocardial infarction during cardiopulmonary by-pass operation in this laboratory have suggested that ischemic injury is most likely to occur in areas of myocardium that are inadequately protected by local and body hypothermia either because of pronounced left ventricular hypertrophy, such as occurs in aortic stenosis, or in areas where coronary blood flow is compromised by disease or by poor vascular supply such as subendocardial areas.[24] The data suggest that posterior-basal ischemia in prolapsing mitral leaflet syndrome may be due to the ballooning of the posterior leaflet, since the T waves became normal following valve replacement. The occurrence of acute ischemic injury to this area of myocardium during operation suggests that it is vulnerable to damage during cardiopulmonary by-pass. This did not appear related to coronary artery disease, since the coronary arteries were grossly normal at operation. Stannard noted that coronary arteriograms were normal in patients with Barlow's syndrome,[25] and no reports of billowing posterior leaflet syndrome have described lesions of the coronary arteries perfusing the inferior left ventricular myocardium.

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Refer to: Dunn RP, Nystrom JS: Association of ectopically produced hyperparathyroidism with hepatoma. Calif Med 118:48-51, Jan 1973

Association of Ectopically Produced Hyperparathyroidism With Hepatoma

ROBERT P. DUNN, M.D., *Stanford*, AND
J. SCOTT NYSTROM, M.D., *Los Angeles*

THERE HAVE BEEN MANY REPORTS of hypercalcemia associated with malignant disease in patients in whom there was no apparent dysfunction of the parathyroid glands at surgical exploration or autopsy, and no bony metastasis. This association has been noted with a wide variety of malignant tumors.[1] Albright and Reifenstein[2,3] first suggested the possibility of non-glandular tumor producing a parathyroid-like hormone in a patient with renal cell carcinoma and bony metastasis in whom hypophosphatemia could not be explained. Connor et al[4] and Plimpton and Gellhorn[5] reported hypercalcemia in patients with malignant disease in whom serum calcium levels fell to normal with removal of the primary tumor. In 1962 Fry[6] first proposed the term *pseudohyperparathyroidism* to describe the syndrome of hypercalcemia and hypophosphatemia without skeletal metastasis in patients with non-parathyroid malignant tumors. Tashjian et al[7-9] reported successful extraction of immunochemically active substance from malignant tumors by use of complement fixation inhibition techniques. Utilizing radioimmunoassay, Sherwood et al[10] later provided quantitative and physical-chemical characterization of the tumor substance. With more recent refinements of assay, Roof et al[11] demonstrated immunological differences between the parathyroid hormone in the serum of patients with primary hyperparathyroidism and that in the serum of some patients with ectopic hyperparathyroidism.

Thus, fall of serum calcium levels with irradiation or removal of malignant tumors, recurrence of the hypercalcemia with recurrence of the tumor, elevated parathyroid-like hormone activity in the serum of these patients, and assay of extracts of such tumors for hormone activity all give evidence that these tumors are capable of synthesizing metabolically active hormones.

Lafferty[1] in his extensive review of "pseudohyperparathyroidism" of malignant disease suggested that one of the following criteria be met for confirmation of this syndrome: (1) absence of radiographic and postmortem evidence of bone metastasis and absence of parathyroid adenoma at surgical exploration or postmortem examination, (2) significant reduction of calcium following resection of tumor, or (3) positive parahormone immunoassay of a neoplasm extract.

We reviewed the data on all previously reported cases of this syndrome associated with primary liver tumors which met one of the foregoing criteria. In addition we present two new cases of this syndrome; in one the tumor was a hepatocellular carcinoma and in the other an adenocarcinoma of the intrahepatic biliary tract.†

Reports of Cases

Case 1. The patient was a 58-year-old Negro man who was referred with history of progressive weakness, lethargy, and a 20-pound loss in weight. He had previously been treated for alcoholic liver disease with ascites and jaundice. He had a long history of alcoholism and of heavy cigarette-smoking. There was no pertinent family history. The patient denied fever, chills, night sweats, cough, chest pain, dyspnea, change in bowel habits or abdominal complaints. On physical examination he appeared older than his stated age. Blood pressure was 110/90 mm of mercury, pulse 82, temperature 37°C (98.6°F) and respirations 18 per minute. There was conjunctival icterus. On examination of the chest the diaphragm was found to be elevated on the right side. The heart was not enlarged, and no murmurs, rubs or gallops were heard. The edge of the liver was three fingerbreadths below the right costal margin in

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Submitted March 20, 1972.

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†Review of slides and tissue diagnosis made by Hugh A. Edmonson, M.D., Chairman, Department of Pathology, USC School of Medicine, Los Angeles, California.

Case 2 was provided by David Potyk, M.D., Assistant Clinical Professor of Medicine, USC School of Medicine, Los Angeles, California.

the mid-clavicular line, and the vertical liver span along the anterior axillary line was 17 cm. Contiguous with the hard, firm edge of the liver was a firm, smooth, non-tender 15 x 15 cm epigastric mass. On rectal examination the prostate gland felt normal. The extremities were wasted.

Laboratory values included the following: hematocrit 38 percent; platelets normal range; leukocytes 8,900 per cu mm with a normal differential. The urine showed urate crystals and was positive for bilirubin. Serum sodium was 130 mEq, potassium 4.2 mEq, bicarbonate 35 mEq, chloride 90 mEq, glucose 74 mg per 100 ml and blood urea nitrogen was 31 mg per 100 ml. Prothrombin time was 90 percent. The albumin was 2.9 grams, globulin 7.1 grams, total bilirubin 3.0 mg, and indirect bilirubin 1.3 mg per 100 ml. Calcium levels were serially greater than 12.0 mg per 100 ml (normal range 9 to 11 mg). Inorganic phosphate was consistently below 2.5 mg per 100 ml (normal range 2.6 to 4.5 mg). Alkaline phosphatase was 5.5 BL units on admission and 2.7 BL units on discharge. The uric acid was 11.3 mg and creatininc 1.3 mg per 100 ml; SGOT 140, SGPT 20, CPK 1.9 and LDH 400 units; serum iron was 69 and TIBC 297 mcg per 100 ml, and iron saturation was 23 percent. Triiodothyronine by uptake was 10.3 percent, and tetraiodothyronine by CPB was 4.6 mcg per 100 ml. Serum protein electrophoresis was normal, and the urine showed no Bence-Jones protein. Hepato-fetoglobulin was positive. An x-ray film of the chest showed a high right hemidiaphragm and no evidence of active or metastatic disease. An x-ray film of the abdomen showed hepatomegaly. An upper gastrointestinal series with small bowel follow-through, a barium enema series and proctoscopic examinations showed no abnormalities. Liver scan demonstrated a filling defect corresponding to the left lobe. Liver biopsy was read as hepatocellular carcinoma. A long bone series, metastatic series, a bone scan and an intravenous pyelogram showed no lesions. The patient was discharged to the oncology service and was readmitted two weeks later with an upper gastrointestinal hemorrhage. He eventually died of pneumonia. Postmortem findings confirmed the presence of hepatocellular carcinoma. No evidence of metastasis was found. The patient was also found to have tuberculous pneumonia. All four parathyroid glands were isolated and found to be histologically normal.

Case 2. The patient, a 36-year-old white man, was admitted initially with complaints of weight loss of 100 pounds, abdominal pain and weakness for five or six months. The pain was mainly in the right upper abdominal quadrant, and it was aggravated by motion or by food. Past medical history was not remarkable except for the drinking of two quarts of beer and a pint of whiskey a day. Family history and review of systems were not significant. On physical examination the patient was normotensive, afebrile, obese and lethargic. There was no jaundice or conjunctival icterus. The liver edge was palpable 3 cm below the right costal margin in the mid-clavicular line, and the spleen was palpated 4 cm below the left costal margin in the left axillary line. Hemoglobin was 12 grams per 100 ml and the hematocrit was 37 percent. Leukocytes were normal in number and differential. Prothrombin time was 75 percent. Electrolytes and fasting blood sugar were normal. Bromsulphalein retention was 13.5 percent. Urinalysis showed pyuria and cast formation but no bacteria. Serial serum calcium determinations were 13.1, 13.5, 12.7, 14.9, and 13.8 mg per 100 ml (normal range 9-11 mg). Inorganic phosphate levels were 2.6 to 2.3 mg per 100 ml. Results of x-ray examination of the chest, barium enema, intravenous pyelogram and survey for metastasis to bone were normal. Repeated cholecystograms failed to demonstrate the gallbladder. Needle biopsy of the liver showed adenocarcinoma. The patient was discharged and treated as an outpatient with 5-fluorouracil and prednisone. Because of progressive weight loss, weakness, and edema, he was readmitted one month later. Physical examination at that time revealed additional massive ascites and three-plus pitting pretibial edema. The blood urea nitrogen was 31 mg, albumin 1.9 grams, globulin 4.5 grams and total bilirubin 4.7 mg per 100 ml. Alkaline phosphatase was 29.6 King-Armstrong units. Serial serum calcium determination was 12.7, 14.1, and 14.6 mg per 100 ml, and prosphate was 2.7 per 100 ml. The patient's condition deteriorated rapidly, and he died 11 days after admission. At postmortem primary adenocarcinoma of the liver was found. Review of the slides showed adenocarcinoma of the intrahepatic biliary tract. No metastatic lesions could be found. The four parathyroids and thyroid gland were found to be histoligically normal.

TABLE 1.—*Review of Case Reports of Ectopically Produced Hyperparathyroidism Associated with Hepatomas*

Reference	Age Sex	Serum Ca^{++}	Serum Phos.	Albumin	AP*	Bone Scan	Parathyroids No.**	Parathyroids Descrip.	Ca^{++} after tumor removal	Hormone assay tumor extract	Tissue Diagnosis
1953[14]	74m	11.5-15.6	2.6-5.0	4.1-5.4	14	NP	3	N	NP	NP	hepatic hemangiosarcoma
1963[15]	52m	10.6-13.2	2.2-3.6	2.7-3.9	22-36	NP	0	—	NP	NP	hepatic cholangiocarcinoma
1965[16]	23m	20.2	4.4	4.3	35	NP	4	N	NP	NP	hepatocellular carcinoma
1968[17]	57m	9.0-25.0	1.3-3.4	1.0-2.7	17-25	NP	2	N	NP	NP	hepatic cholangiosarcoma
1970[18]	56m	10.0-17.6	1.4-2.7	—	20-40	N	3	N	↓	+	intrahepatic biliary adenocarcinoma
1971[12,13]	—	—	—	—	—	—	—	—	—	—	hepatocellular (3), hepatoma (1)
Case 1	58m	10.5-12.4	2.2-2.6	2.7-2.9	9-19	N	4	N	NP	NP	hepatocellular carcinoma
Case 2	36m	12.7-14.9	2.3-2.6	1.9	29	NP	4	N	NP	NP	intrahepatic biliary adenocarcinoma

*converted to King-Armstrong units
**at surgical exploration or postmortem examination
NP—not performed
N—normal

Abbreviations

BL	**Bessey-Lowry units**
SGOT	**serum glutamic oxalic transaminase**
SGPT	**serum glutamic pyruvic transaminase**
LDH	**lactic dehydrogenase**
TIBC	**total iron-binding capacity**
CPK	**creatine phosphatase**
CPB	**competitive protein binding**
PTH	**parathyroid hormone**

Discussion

Search of the literature revealed five previously recorded case reports of hypercalcemia associated with malignant liver tumors which satisfied the criteria mentioned above. In addition, Riggs et al[12] included four cases of hepatoma in a recent report. Three of these were hepatocellular carcinoma, and the fourth was an undesignated hepatoma.[13] No additional data were given in the report concerning these patients.

Data from the previously reported cases and the present case reports are presented in Table 1. Of interest is the fact that all cases involved male patients.

In evaluating hypercalcemia, the following disease processes and diagnostic procedures should be considered: (1) milk alkali syndrome—history of alkali intake, (2) vitamin D intoxication—review medications, (3) immobilization—paralysis or external fixation by a cast, (4) hyperthyroidism, hypothyroidism—protein-bound iodine, radioactive iodine uptake, tetraiodothyronine by CPB, (5) bone disease—radiologic bone survey, bone scan, (6) sarcoidosis—lymphadenopathy, skin lesions, serum proteins, chest film, (7) adrenal insufficiency—17-OH steroids, (8) renal disease—creatinine clearance, intravenous pyelogram, (9) multiple myeloma, leukemia—serum protein electrophoresis, Bence-Jones protein, bone survey, bone marrow. Even with these diseases ruled out, the possibility of occult malignant disease with parathyroid-like activity should be thoroughly winnowed before consideration is given to exploration of the parathyroid glands.

Lafferty[1] pointed out the following items as weighing heavily toward the diagnosis of ectopic hyperparathyroidism: (1) presence of anemia, (2) elevated sedimentation rate, (3) weight loss, (4) recent onset, and (5) serum chloride less than 102 mEq per liter. The variety of tumors which produce PTH-like material occur in the fol-

lowing descending order of frequency: lung, kidney, colon, bladder, and ovary. The two cases herein reported point out the necessity of considering hepatic tumor among these.

Summary

Two cases of ectopically produced hyperparathyroidism associated with hepatoma are presented and previously reported cases of this syndrome are briefly reviewed.

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Government and Medicine

California Coroners' Patterns

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EACH COUNTY IN CALIFORNIA has a coroner or medical examiner charged with the responsibility of investigating and evaluating deaths that are, or possibly are, other than natural, and also with the responsibility of discovering and preserving evidence needed in any incident litigation or trial which may result from that death. In general these officers operate under the authority of California Government Code 27491 with additional responsibilities under various sections in the Penal Code and the Health and Safety Code. Interpretation of the law, and thus the method of carrying out these responsibilities, is to some extent in the hands of the coroner or medical examiner, utilizing the district attorney and county counsel for legal advice and opinions in areas of question.

While there are obviously many areas of uniformity of activity in these functions, there is significant variation in certain aspects. With the cooperation of the California Coroners' Association, the Forensic Pathology Committee of the California Society of Pathologists has attempted to survey these activities and evaluate variations. It would be impossible to do this in depth without substantial funds, which were not available. However, even the somewhat superficial survey here reported, which has been made by physicians familiar with the patterns in various counties with the whole-hearted cooperation of the coroners themselves, has revealed much that we believe can be of value.

A simple questionnaire devised by the Forensic Pathology Committee was submitted to the Executive Committee of the California State Coroners' Association. It was approved and endorsed by its executive committee and by its president, William A. Scott.

In four counties the coroner or medical examiner is a physician. In Los Angeles, Santa Clara and San Francisco counties the coroners are forensic pathologists. In Marin County the coroner is a surgeon who had had specialized training and experience in coroners' offices before his election. In most counties the coroner is an elected officer. In 31 counties the sheriff is the coroner. In the remainder, the office may be filled by a mortician or a lawyer and occasionally the coroner is a layman. In some counties, even when these offices are separate, the sheriff is designated to serve as coroner in periods of absence or disability of the coroner. The coroner is usually the public guardian and public administrator also, and in San Benito County he is, in addition to all this, tax collector and civil defense director.

The coroner usually appoints his deputies. In several counties, particularly the larger urban ones, there is an examination for selection of dep-

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uties, and specialized qualifications have been established. In many counties the appointments are at the discretion of the coroner, without clear-cut guidelines for selection. Deputies chosen generally have had some investigative experience; this is a requirement in those counties which have written qualifications. Rarely, however, have the deputies had any medical experience.

Coroner Training

In general, the deputies are trained "on-the-job" under the guidance of an experienced deputy, with consultation with the coroner and pathologists being readily available. Medical training of deputies has been sketchy. There have been several brief symposia for this purpose, but they have been rare and have not covered much of the state. For four years a Coroners Investigator's Institute giving 80 hours of instruction in a two-week period has been available at Yuba College. This is to be moved this year to either Merced or Stanislaus County, Yuba continuing with a more intensive Homicide Institute. These courses deal primarily with the investigative rather than the medical aspects. A Forensic Pathology Institute has recently been organized in Alameda County by the pathologists in the area. Curricula for training coroner's personnel in both investigative and medical fields are being developed there.

Recently organized and now available is a basic Law Enforcement Institute given annually in several of the larger community colleges. This is an eight-week course, with a full eight-hour daily program leading to a basic certificate in Peace Officers' Standards of Training. It is hoped that more coroner's deputies will be allowed to take such a comprehensive course in the future, even though it may involve quite a significant expense to the county authorizing such training.

In many counties, especially the larger ones, the coroners' office policies describing criteria for the evaluation of cases are printed in a manual which contains amplifying and explanatory material. In other counties, little is written except for the listing of cases required by California Government Code Section 27491. There is only sketchy dissemination of this information among the medical profession, although some counties are making such instruction a part of their indoctrination programs for new members of their medical societies. Because physicians often are active in more than one county and policies differ in various counties, this is a source of confusion. For example, there is great variation with regard to the determination of what constitutes a death "without a physician in attendance." We conclude that there is a definite need for greater physician awareness of the requirements of the law and the local policies in this regard. A statewide manual for uniform policy would be most helpful.

In most counties about 30 percent of all deaths fall into the jurisdiction of the coroner. This varies from reported levels of 17 percent to 60 percent. In cases accepted as coroner's cases, the death certificate to be signed by the coroner, autopsy is performed in 90 to 100 percent in most counties, dropping to as low as 40 percent in a few counties. Geography seems to play little part in the determination of when to carry out autopsy. Rather, the decision seems to depend on finances and the opinions and policies of the county coroner.

Autopsy by Pathologists

In nearly all counties, the autopsy is performed by a local pathologist and, even where no pathologist is available, tissues are sent to a pathologist with the report of the physician doing the gross autopsy. In homicide cases a forensic pathologist is always utilized even in those counties having no local pathologists to perform the gross examination.

In the larger urban counties central morgues have been created. In most counties, the facilities of the local mortuaries are used, and are considered acceptable, although obviously a centralized facility offers many advantages. In many such cases autopsy is not done until after vascular embalming. In at least two of the larger counties, mortuaries are utilized in the more remote areas rather than transport of the bodies to the central morgue. One small county lacks even a mortuary and in coroner's cases bodies from this county are, of necessity, transferred for autopsy to the nearest available facility, which happens to be in Nevada.

Several coroners have expressed the desire to have a central morgue, but generally they do not wish this to be part of the county or district hospital. The only coroner's office which classed its facilities as unsatisfactory uses the local hospital for autopsy cases, although it is planning a cen-

tral morgue to eliminate this dissatisfaction. On the other hand, several coroners are associated with local hospitals and feel that the arrangement is quite satisfactory. In general, it would appear that physicians and hospital administrators are, on occasion, apt to make requests or demands which are less than reasonable, in light of the requirements and limitations of the law under which the coroner must act. Obviously a physician coroner is in an advantageous position in using local hospitals, and a mortician or sheriff coroner at a disadvantage in dealing with hospital and medical personnel.

The extent of the autopsy, including the questions of head examination, microscopic study of tissue, and the use of toxicologic study is generally decided jointly by the coroner and the pathologist; the district attorney may also assist in establishing policy regarding the extent of the autopsy. Only slight difficulty is reported in this respect in examination of embalmed bodies; generally, necessary blood specimens are withdrawn before embalming and if other toxicologic studies are essential autopsy also is done before embalming. Vascular embalming obviously forecloses the possibility of bacteriologic cultures and virologic studies. In homicide cases the bodies are uniformly examined before embalming is done. Blood and specimens obtained in the hospital before death are often invaluable in supplying needed answers to toxicologic questions, and often to bacteriologic questions as well. It is possible that laboratory work done before death, and in particular toxicologic findings, are properly privileged and confidential information, which would limit the public use or knowledge of these pre-mortem findings.[1] Facilities for any bacteriologic study are poor to non-existent in most mortuaries. Smears and special stains on tissue sections seem to be about all that can be expected in any but the most unusual cases.

X-ray facilities are also lacking in most coroners' facilities. Local hospitals supply this service when it is deemed essential, but it is used somewhat rarely in view of the difficulty and expense, as well as the distaste of most hospitals for bringing in bodies, especially during the hours when many patients may be in the department. X-ray examination is usually reserved for search for bullets which cannot be easily located, and for suspected homicide cases. It is generally felt that x-ray services could be used advantageously in many other cases.

Urban centers with central morgues often have facilities for doing their own laboratory and toxicologic studies, microscopic slide preparation, photography, and, perhaps, bacteriology. In many counties local pathologists perform the autopsies and do all or some of the ancillary studies in their own clinical laboratory facilities. In counties lacking a local pathologist, or clinical laboratory, specimens of tissue and body fluids are sent by mail to an appropriate laboratory, usually in a nearby county. Close consultation between the coroner, the autopsy surgeon and the toxicologist or consultant pathologist usually makes this arrangement reasonably satisfactory. Obviously, the service could be improved if fewer persons were involved, but the compromise is a practical necessity. Specialists are used, however, even in these remote areas when the magnitude of the case justifies, particularly in homicide cases.

Autopsy Reports

Reasonably complete autopsy reports are prepared in every reporting county. Such reports are usually available within a few days, rarely more than three weeks being needed to complete all studies and reports. In at least one county the reports are recorded on tape, and are transcribed only as needed. The complete report generally contains a summary of the investigation by the deputy coroner, the gross and microscopic studies, and the toxicologic and laboratory findings. These reports are legally public property, and as such are usually made available to other agencies, attorneys, local hospitals, and physicians. In some counties toxicologic results and investigator's reports are not sent with the autopsy report unless specifically asked for. A small fee may be charged for the reports.

Tissue blocks and microscopic slides are filed permanently in either the central facility or in the custody of the local pathologist who performed the autopsy. Toxicologic specimens and additional gross tissues are stored for variable periods. In some counties this may be only until the autopsy report is complete. In many counties these materials are stored for a minimum of one year, in others it is left to the discretion of the pathologist. In any event, space and specialized refrigeration requirements encourage early

[1]Rose, E. T. American Journal of Clinical Pathology. 57, No. 2 pp 144-155. February, 1972

disposal of excess tissue and toxicologic material. Longer storage is deemed desirable by forensic pathologists, probably a year being the minimum acceptable time, with material in selected cases being stored even longer.

Expenses of Autopsy

The expenses are borne by the county, and there are wide variations in the costs for the services involved. The coroner's salary is set by the county board of supervisors, as are those of his deputies and secretarial personnel. In larger counties, especially those with central facilities, the autopsy surgeons, toxicologists, and other technical personnel may also be on a regular monthly salary. In a few areas, local pathologists have negotiated a flat annual fee for covering all the medical aspects of the coroner's activities. In most counties, however, the coroner has negotiated a fee structure with the local pathologist which covers his services, regardless of the extent of evaluation; or it may be a series of fees covering the gross autopsy, with increments for head examination, microscopic study of tissues, and laboratory and toxicologic studies.

These fees reflect the availability of personnel with the ability to perform the various studies. Greatest economies are possible in areas with centralized facilities; the greatest expense occurs in remote areas where specialists must be brought in from distant centers. For example, an urban area with a large number of coroner's autopsies may be able to obtain all necessary medical and laboratory studies on an annual contract averaging less than $60 per case. A remote, small county may incur expenses of up to $375 per case; and this cost may be increased if extensive toxicologic and laboratory services are involved. In most counties, however, the fee for medical studies totals between $75 and $150 per case, with the pathologist often bearing the expense of routine toxicologic and microscopic study.

Selection of Cases for Autopsy

Rising costs and limitations on county budgets have made both coroners and forensic pathologists question the need for autopsy in a high percentage of autopsies. It would seem that a significant number of cases could be certified quite safely without autopsy. For example, many cases of senile degenerative diseases, or of known malignant disease become coroner's cases only because the persons who died had not had medical attention within the last week of life. This may apply even in cases of death in convalescent hospitals or rest homes where adequate investigation can reasonably rule out foul play.

Industrial accidents pose special problems, particularly in view of the large number of "heart attacks" which involve litigation because of alleged industrial causation or aggravation. In the case of certain groups, such as police and fire department personnel, such deaths are established as "industrial" *by law*, with no need for medical opinions. In any event, a complete autopsy should be done in such cases, including an examination of the central nervous system because of possible legal requirements in this often neglected and forgotten sphere.

The coroner's inquest is used rarely. San Francisco and Los Angeles counties hold about 100 to 150 inquests each year, but most other counties report only one or two a year. Several counties said that they never hold inquests. When an inquest is held, there are usually few expenses, with the witnesses receiving no fee (or only a minimal fee), depending on time and travel involved.

Material for Scientific Research

There is great variation in policies regarding availability of reports and tissue slides for review by physicians, especially when this is for scientific and research purposes. Generally, most coroners will authorize release of slides for study by any legitimate consultant, such as a pathologist reviewing the material for defense purposes, or to industrial accident carriers. Scientific and research purposes constitute an entirely different problem, which is not authorized under present law, and coroners are reluctant to release material for such purposes. Before the material can become routinely available, changes in public law will be necessary to authorize this use and to protect the coroner from liability.[2]

In addition, all coroners are aware of the frequency of requests for material for scientific and research purposes. Often to comply with these requests would involve a direct violation of laws. Even when only minor service is requested a significant expense or labor demand might be en-

[2]Assembly Bill 1194 (Quimby) currently before the California Legislators is designed to allow the use of autopsy material for scientific, educational, and research use.

tailed, often without offer or mechanism for compensation. Although the coroner may be willing to cooperate in some circumstances, the autopsy surgeon may be reluctant because of other demands on his time. Research must not hamper the pathologist in any way in obtaining data and material necessary for the medico-legal aspects of each coroner's autopsy. Demands of research create a conflict of interests, and a distraction from the task at hand. If we are successful in getting laws modified, the use of coroner's material can be legally extended to include scientific and research purposes. However, the medical profession must remember and respect (a) the myriad of demands and pressures on the coroners and on their autopsy surgeons, (b) the basic duty of the coroner, which will always take precedence over research, (c) the pressures from morticians, and (d) the rights of the next-of-kin.

Currently, release of material is authorized readily only to those involved in litigation associated with the death in question. Even here, there is variation in coroners' policies. Most coroners will authorize the mailing of slides to legitimate consultants. Often the slides are in the custody of the autopsy surgeon, who may be reluctant to relinquish them because of the danger of loss. But as the tissue blocks are retained and slides can be easily duplicated if necessary, fear of loss seems an unjustifiable reason. It is probable that some coroners simply are not aware that slides are easy to duplicate.

All coroners will release slides upon a court order, but obtaining such an order seems an unjustifiable expense and a burden for already overworked courts. It is the opinion of most coroners, and of the Forensic Pathology Committee, that slides upon which the microscopic descriptions are based are just as much public property as the report itself.

In the opinion of forensic pathologists, coroners are generally highly motivated persons trying sincerely to carry out their responsibilities well under trying physical and economic circumstances. This motivation is probably at least as important in determining the quality of their performance as any specialized medical or legal training. Medical requests and public demands often subject the coroner to unfair and improper pressures. More physician awareness of the responsibilities and limitations of coroners is essential.

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Refer to: Burr BD, Hess GH: More primary physicians—The department of family practice at UC, Davis, meets the challenge (In the Forefront). Calif Med 118:57-61, Jan 1973

In the Forefront

More Primary Physicians

The Department of Family Practice at UC, Davis, Meets the Challenge

Bill D. Burr, M.D., and George H. Hess, M.D., *Davis*

Much has been written about the "health care crisis" in our country. Opinions vary from "There is no shortage of physicians, only maldistribution," to "there is a true crisis in health care delivery because of doctor shortages."[1]

It is established that there is a critical shortage of primary care physicians in California.[2,3] Many communities have no physicians, and those that do often see the doctor leave for a variety of reasons with no replacement in sight.

The problem of supplying medical care to rural communities is multi-faceted. Many surveys have been done to ascertain the reasons why physicians leave rural practices.[4] Among the reasons most often cited are overwork, inadequate professional stimulation, inability to get away for post-graduate education, inadequate hospital or office diagnostic facilities, and dissatisfaction with rural living.

For a training program to produce more family physicians and ignore the factors which drive the rural physicians to urban areas would be unrealistic. Since it is obvious that physicians' attitudes are quite fixed by the time they finish an internship, a great deal of energy should be spent at undergraduate levels. Students basically learn from the physician models to whom they are exposed. Thus, introduction into family medicine should be begun during the first year by exposure to physicians doing front-line medicine. Methods need to be devised to allow students to learn first-hand the advantages of rural practice and rural living.

Along with introducing the student of medicine to family medicine, the following areas need to be stressed:

1. *Group Practice.* Unless a rural medical center develops a "critical mass" of manpower, all of the disadvantages of rural practice will be overwhelming. A minimum of two doctors appears to be essential to allow coverage for rest, recreation, and post-graduate education.

2. *Team Approach.* By utilizing the health care team approach, the physician will have more free time.[5,6,7] Nurse practitioners and physician assistants will care for many medical problems within their competence that usually take up many hours of the physician's day. Satellite offices in small communities can be staffed by paramedical personnel. They can do the medical triage and handle many minor problems very efficiently. One of the physicians could travel to the outlying office one or two afternoons a week to see patients with diagnostic problems that have been initially evaluated by the paramedical practitioners. Problems beyond the ability of the

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practitioners could be referred immediately to the central office.

3. *Rural Medical Center.* When possible, the group practice can operate most efficiently near a center, such as a community hospital, where diagnostic facilities and trained personnel are available. Duplication of laboratory and x-ray facilities can be avoided, and because of higher volumes, better equipment and more experienced personnel can be utilized. Having the hospital nearby will eliminate the many hours of driving that isolated rural physicians must now do.

4. *Continuing Education.* A great effort should be made for the training program to provide means for the practicing physician to be involved in a strong continuing education program. Visiting professors, closed television programs, locum tenens and preceptorship programs will keep the practicing physician involved in teaching and exposure to the recent advances in medicine. Students and residents should plan their life style to include at least four weeks a year of postgraduate education.

The University of California, Davis School of Medicine, through the Department of Family Practice, is dedicated to meeting the needs in primary care for Northeastern and Central California.

The Family Practice Residency Program

The School of Medicine of the University of California at Davis was authorized by the Regents of the University of California and the State Legislature in 1963. C. John Tupper, M.D. was appointed dean and began work in Davis in February 1966. The first class of 48 medical students was admitted in September 1968 and was graduated June 15, 1972.

The Department of Family Practice was established in 1970 with the appointment of Len Hughes Andrus, M.D. as professor and chairman in October of that year. The Family Practice Residency Program was approved by the Council on Education, American Medical Association, in May 1971.

Philosophy and Purpose Of the Program

The family physician, practicing both scientific and humanistic medicine, is a personal physician oriented to the whole patient, his family, and the community in which he lives. The residency program is dedicated to producing a physician who is an effective member of a health care team whose training will be relevant to the needs of society now and in the future.

The family physician will serve as a physician of first contact with the patient and provide a means of entry into the health care system. By means of a comprehensive and extensive training program of family medicine, the family physician will provide personal medical care that will handle 80 to 90 percent of all the patients' needs. He will provide entry for the patient into secondary care with the specialists in other fields of medicine, assuring that the patient will have continuity of care following consultation. The family physician will assume responsibility for the patient's comprehensive and continuous health care and act as a leader or coordinator of the health care team designed to provide family oriented care. He will accept responsibility for the patient's total health care needs within the context of his environment, and will stress preventive medicine. The family physician will provide leadership in health affairs within the community, be committed to evaluate new organizational methods of care, and introduce technical advances which will result in improved patient care.

The "New Look"

The Family Practice Residency Programs differ from previous general practice programs in a variety of ways. The older general practice residency programs were inflexibly hospital-centered in the traditional departments with unstructured ambulatory experience in the emergency room and general out-patient clinic. The Family Practice Residency Program stresses the continuity of family oriented care throughout a three-year residency program. During this time the emphasis on in-depth hospital training is at its maximum during the first year, and gradually decreasing during the remaining two years. Increasing time is spent in the ambulatory area throughout the second and third years where the family physician develops the skills necessary to provide for the majority of his patients' needs.

Unique Features of the Program

Features peculiar to the Family Practice Residency Programs are the following:

1. *The Family Practice Model Unit* is the hub of the Family Practice Residency Program. It provides a setting similar to the private offices of practicing physicians. Physicians from the community serve as preceptors in the Family Practice Model Unit to help the residents understand the practice of ambulatory medicine and participate in an educational exchange with the residents. The model unit also serves to provide experience for the resident in understanding medical records, insurance forms, economics, and management of paramedical personnel.

2. *The Problem-Oriented Record*, or the "Weed System," is required in the Family Practice Model Unit. The Problem-Oriented Record is a system of collecting data pertinent to the patient's multiple problems, objectively evaluating this data and formulating an appropriate diagnosis and therapeutic plan. The Problem-Oriented Record also provides a means of therapeutic audit that folows a logical pattern and will be a vehicle for the up-grading of quality of medical care.[8,9]

3. *The Team Approach.* The resident will work within the model of a group practice, where he will be the leader of a health care team consisting of a student nurse practitioner, social worker, visiting home nurse, and other out-reach workers. The resident will become familiar with delegating some jobs to other team members to increase his efficiency, and eventually, when he is in practice, provide him with time to concentrate on the more difficult diagnostic problems and pursue continuing education.

Multi-disciplined conferences are planned which will demonstrate the team approach. The resident will manage these conferences, with participation by the nurse practitioner, the social worker, the visiting home nurse, and any other health care provider necessary for the total care of the patient.

4. *The Locum Tenens Program.* As the resident completes his second year, he will select a locum tenens for a six-week period. The first two weeks will be spent working with the local physician. During the last four weeks, while the resident takes over the practice, the local physician will return to the Sacramento Medical Center for post-graduate training. During this time, the visiting physician will be actively involved as a preceptor in the Family Practice Model Unit, thus ensuring a close relationship between practicing physicians and the Family Practice Residency Program. The resident will be encouraged to take his family with him while serving locum tenens to provide them some exposure to the advantages of living in rural communities. They will have a chance to become acquainted in the town, evaluate the school systems, and gather a great deal of information to assist them in selecting a place to practice.

Upon returning from the locum tenens, the resident will be expected to evaluate his own performance and will be counseled regarding the evaluation of his performance by the physicians in the locum tenens setting. The remainder of his residency electives are then selected to provide further training in fields in which he has found he has special needs.

5. *Research Project.* Each resident will be expected to participate in a research project during the last two years of the residency program. Although there will be no strict guidelines for the research projects, it is anticipated that health care delivery systems will be investigated and record systems and disease coding devised to provide a means for effective clinical research in ambulatory medicine.

6. *Flexibility of the Program.* An important feature of the Family Practice Residency Program is the variety of pathways that a resident may choose. It is desirable to capitalize on previous training and experience of the resident and to provide a learning experience that is relevant to his future needs. If the resident has already chosen the location in which he desires to practice, the particular needs of the patients and physicians in that community will be examined and the training program tailored to meet them.

The Family Practice Residents are assigned in pairs on the major services at the Medical Center. This ensures that one resident will be available every other afternoon to see his patients in the Family Practice Model Unit. The other resident will be available on the ward to take both to care of the resident's patients and to handle any emergency situations that may come up. This schedule obviates the problem of unavailability due to the requirements of the Family Practice Clinic and it has been enthusiastically supported

by the other departments in the Medical Center.

7. *Family Practice In-Patient Service.* The Department of Family Practice operates an in-patient service in the Sacramento Medical Center Hospital. This Family Practice Service is located in a geographically separated area, but in addition it has some beds scattered throughout the other services in the hospital. Problem-oriented records are used on the in-patient service, and the nurses on the Family Practice ward assume an expanded role and are intimately involved in the care of the patients. The ward provides an exemplary vehicle for the delivery of comprehensive health care by the entire health care team. The Family Practice resident admitting a patient to this ward continues the role of the primary physician, as no interns are utilized by the service. All admissions to the Family Practice ward must be approved by the Family Practice resident on call.

8. *Community Medicine-Public Health Rotation.* The community medicine and public health rotation is of two months' duration and it is expected to enable the resident to familiarize himself with the various resources of the city, county and state. A wide variety of interesting electives are available as well as experience in one of the Health Department satellite clinics.

9. *Curriculum Content.* The core content of the Family Practice Residency Program includes the basic knowledge required for comprehensive primary care in the fields of medicine, pediatrics, obstetrics and gynecology, and surgery. The Family Practice resident is considered as a regular resident of the rotations to which he is assigned. This educational experience is supplemented by the continuous exposure in the Family Practice Model Units to the variety of problems of ambulatory patients. The surgical experience for the resident will be tailored to meet the needs of his proposed practice style. It is anticipated that most family physicians will not be undertaking major elective surgical operations, but there may be an occasion when family practitioners in remote areas must be capable of emergency life-saving operations.

Since it is recognized that psychiatry plays an important part in the delivery of primary care, training in psychiatry for Family Practice residents continues throughout the three-year period. The residents are assigned a psychiatrist who relates to them throughout the three-year residency program and is active in the multi-disciplinary Family Practice conferences, stressing the emotional aspects of illness as it relates to the entire family constellation. In addition, special seminars are planned to deal directly with the problems of sex education, marriage counseling, office psychotherapy, psychopharmacology, and the like.

A seminar will be conducted in Business Management. This will include topics such as personnel management, medical economics, malpractice, personnel selection and interviewing techniques, licenses, and insurance. This seminar will be conducted by experts from the business community and consultants in medical economics.

Preceptors from the local community volunteer time to be involved in the teaching program at the Family Practice Model Unit. The preceptors will stress the practical aspects of ambulatory medicine as practiced in their offices, and provide a realistic model for their residents to follow. The preceptors also participate as attending staff for the Family Practice In-Patient Service.

Evaluation

The Family Practice Residency Program is under continual evaluation. The preceptors evaluate each resident with whom they work, and in turn, the residents evaluate them. Medical audits will be conducted on a continuing basis to monitor the quality of care. Residents will be expected to keep records of the types of clinical experiences they have had. They will be evaluated on a quarterly basis by the Program Director.

Future Projects

It is the desire of the Department of Family Practice to develop a strong post-graduate education program that will provide opportunities for practicing family physicians to maintain or increase their competency. It is proposed that in the future the Department of Family Practice provide a team of physicians to go to distant communities to relieve solo or isolated physicians so that they may return for post-graduate education. This will also provide a means of front-line medical experience for residents and staff members. By developing affiliated Family Practice Programs, it is anticipated that most of the health care workers will come from the local communities. It is planned to provide the high schools

and junior colleges with consultants from the Department of Family Practice to explain the career potentials in family medicine. Through this effort, students may become well informed of the Family Practice potential in the field of medicine, and be stimulated to enter the broad but challenging field of primary care.

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APPENDIX:—*Resident Schedules for Family Practice Residency Program at UC, Davis, School of Medicine*

Month	*First Year*	*Second Year*	*Third Year*
1	Medicine	Medicine	Emergency Room
2	Medicine	Medicine	Locum Tenens
3	Medicine	Medicine	Locum Tenens
4	Med. E.R.	Pediatrics	Pub. Health & Comm. Med.
5	Pediatrics	Pediatrics	Pub. Health & Comm. Med.
6	Pediatrics	Pediatrics	Electives[1]
7	Surgery	OB-Gyn[2]	Electives[1]
8	Surgery	OB-Gyn[2]	Electives[1]
9	Surgery	OB-Gyn[2]	Electives[1]
10	Surg. E.R.	Surgical Elective[3]	Electives[1]
11	OB-Gyn	Surgical Elective[3]	Research
12	Elective	Psychiatry	Electives[1]
	½ day per week in Family Practice Clinic	Three half days per week in the Family Practice Clinic	Three half days per week in the Family Practice Clinic

1 = Electives in X-ray, Neurology and PM&R are strongly suggested
2 = Three months of OB-Gyn or resident may elect 2 months of medical gynecology and one month of elective
3 = Orthopedics, ENT, General Surgery, Anesthesiology, Ophthalmology, Urology may be considered

Refer to: Schoen EJ, Erickson RJ, Barr G, et al: Role of pediatric nurse practitioners as viewed by California pediatricians (The Health Care Team). Calif Med 118:62-68, Jan 1973

The Health Care Team

The Role of Pediatric Nurse Practitioners as Viewed by California Pediatricians

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■ *A single-mailing questionnaire surveyed attitudes of members of District IX, American Academy of Pediatrics (California) toward the role of the pediatric nurse practitioner* (PNP). *Responses from 568 members (53%) represented a broad range of age, practice type (58% group, 25% solo, 17% "other"), geographic location, and opinion. The most favorable attitudes toward* PNP *use were expressed by young pediatricians in large-group and "other" categories; least favorable were solo practitioners older than 60 years. Practice type was more important than age. Most respondents expressed the opinion that a pediatrician-*PNP *team approach would enrich both professions, and that parental acceptance of the* PNP *was likely; but that* PNP *use would not reduce costs. Majorities favored the concept of the* PNP *as part of the practice team but under constant pediatrician surveillance: seeing the patient for part of the visit and participating under supervision in care for minor illness, but not replacing the pediatrician even in well-child care. Some* PNPs *hope for a more independent role on the pediatrician-*PNP *team. Modification of both pediatrician and* PNP *ideas appears requisite to a team approach that will satisfy both professional groups and the public.*

INCREASED USE OF ALLIED HEALTH PERSONNEL is being widely recommended as a means of improving the delivery of health care to the people of the United States. Surveys by Yankauer and colleagues indicated that a majority of 155 responding Massachusetts pediatricians[1] and most of some 6,000 pediatricians throughout the nation[2] were willing to delegate numerous specific patient-care tasks to a variety of allied health personnel, from registered nurses to receptionists. Their surveys were not specifically concerned with the pediatric nurse practitioner (PNP), prob-

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ably the most firmly established and clearly defined allied health professional currently available to extend primary child health care.[3,4] At least 18 training programs for PNP's have been started in this country, and it is estimated that 350 PNP's have been trained since 1965.[5] A joint statement of the American Academy of Pediatrics and the American Nursing Association defines the category of PNP and offers guidelines of functions, responsibilities, and education for this role.[6]

Initial reports[3,4,7-11] indicated that the PNP was readily accepted by patients in a variety of pediatric practice situations; that the PNP was professionally and economically beneficial to the practice, and appeared to be stimulated by the new relation to patient and pediatrician. Some later observers,[12,13] however, have raised questions about patients' and physicians' acceptanee of the PNP in pediatric practice.

Since acceptance by the physician is important to any role on the health-care team, we conducted a survey of California pediatricians' attitudes toward the PNP in which we tried to elicit a definition of these pediatricians' concepts of an appropriate role for the PNP in private practice. In January, 1971, the Executive Committee of the California Section (District IX) of the American Academy of Pediatrics helped sponsor the survey reported here. The findings indicate that there may be some disparities (1) between the pediatrician's theoretical acceptance of the PNP concept and his idea of the PNP's practical role, (2) between the attitudes toward PNP's held by pediatricians in various types of practice and age groups, and (3) between the role of the PNP as envisioned by the majority of these California pediatricians and as anticipated by PNP's themselves.

Procedure

A questionnaire (Appendix) was designed by a social psychologist working with pediatricians with the goal of obtaining measures of pediatrician acceptance or nonacceptance of the PNP. The pediatrician was requested to respond to each of 37 statements by indicating "agreement," "strong agreement," "disagreement," or "strong disagreement." Some of the statements explored whether the pediatrician believes that PNP's will enhance care for patients, will help to lessen the cost of health care, or will be accepted by physicians and patients. Others probed the pediatrician's concept of the PNP role in private practice, and of PNP aeceptance in group and in solo practice. The questionnaire was made brief enough to encourage maximal response to a single mailing, rather than attempting to achieve maximal numbers of responses by three successive mailings, as was done by Yankauer and assoeiates.[1,2]

To develop the questionnaire, ten pediatricians and ten nonphysicians familiar with the medical field (including two psychologists, three psychology graduate students, two social workers, two registered nurses and one medical secretary) rated each statement as "for" or "against" the concept of PNP involvement in pediatric practiee. Statements rated for or against such involvement by 75 percent or more of the 20 raters were so designated for study purposes. A total of 12 statements were thus rated "positive" and 18 were rated "negative." If fewer than 75 percent of both rating groups agreed about the positive or negative character of the statement, it was used only for the information it furnished, not for general attitudinal survey. Seven questions fell into this latter category. The judges were employed only to assign questions to "positive," "negative," or "information only" categories.

A system for scoring answers made by respondents was then devised to quantitate the over-all response to the PNP concept; since 12 statements had been rated "positive" and 18 "negative," a score of 36 was assigned to the unmarked questionnaire. Agreement by a respondent with a favorable statement added 3 points to this score; agreement by a respondent with a negative statement subtracted 2 points. Thus, if a respondent agreed with all of the 18 negative statements and disagreed with all of the 12 positive statements, his total questionnaire would be scored 0; the converse would yield a score of 72. For scoring purposes, "strongly agree" and "tend to agree" were both considered agreement, while "strongly disagree" and "tend to disagree" were considered disagreement with the statement.

In January 1971, 1150 questionnaires were mailed out by the American Academy of Pediatrics in a single mailing to all District IX members. To maintain anonymity, questionnaires were unmarked but they asked the recipient's age, sex, years in practice, type of practice (solo, group and group size, or "other"), and place of practice (rural, urban, suburban); and responses were separated by postmark into Northern and

TABLE 1.—*Type of Practice by Age Group of 556 Responding California Pediatricians for Whom Both Data Were Available**

Age in Years	*Number in Group*	*Percent of Total*	*Type of Practice*				
			Solo	*Small Group†*	*Medium Group‡*	*Large Group§*	*Other¶*
			%	%	%	%	%
<40	143	25.7	19.6	16.7	25.4	21.0	17.4
40-49	246	44.3	21.4	18.9	21.0	17.2	21.4
50-59	111	19.9	31.8	16.4	29.1	12.7	10.0
60+	56	10.1	41.2	21.6	17.7	7.8	11.8

*Either age or type of practice was not indicated by 12 respondents.
†Two pediatricians.
‡3-5 pediatricians.
§Six or more pediatricians.
¶Mainly public health, research, administration, teaching.

Southern California according to a line drawn on the map across the northern boundary of the Tehachapi mountain range.

Results

After mailing, it was learned that 45 of the questionnaires had been sent to affiliate members of the Academy who are in other specialties, who were on leave, or were in emeritus status; the few replies received from these affiliates were not considered. Of the remaining 1105 questionnaires, 568 (about 53 percent) were returned, representing a majority of California pediatricians and including pediatricians in all age groups with a broad representation of types of practice, shades of opinion, and geographic locations. It should be emphasized that the results reported represent opinions only of respondents, not of all California pediatricians.

Description of Responding Pediatricians

The distribution of respondents according to age and type of practice is shown in Table 1. Their mean age was 47 years; the mean number of years in practice was 17. Eleven percent were women. About an equal number responded from Northern (241) and from Southern (262) California (65 postmarks were not legible), reflecting the distribution of pediatricians in the state. Responses to the questionnaires showed no difference in attitude between Northern and Southern California pediatricians. Only 3 percent characterized their practice as rural. Many of the others had difficulty in deciding whether their practice was urban or suburban, so that these two categories were combined. Fifty-eight percent of the pediatricians were in group practice, 25 percent in solo practice, and 17 percent in "other" categories, mainly public health, research, administration, or teaching. Of the group practitioners, most (23 percent of the total respondents) were in "medium-sized" groups, defined in the questionnaire as three to five pediatricians; 18 percent were in two-pediatrician groups, and 16 percent in "large" groups (six or more pediatricians).

Responses to Individual Statements

1. Role of the PNP, and Relation to the Pediatrician:

Pediatricians overwhelmingly agreed (96 percent) that in order to function successfully the PNP would have to be fully accepted by the physician. Eighty-six percent stated that the PNP should only supplement the pediatrician by seeing each patient for a portion of the visit; 86 percent, that the PNP should not totally replace the physician in well-child care. However, 75 percent indicated that the PNP could take part in the care of children with minor illness. Seventy-one percent replied that utilization of PNP's by pediatricians would lead to enrichment and expansion of both professions, but 68 percent believed that the PNP should be under the constant observation of the pediatrician.

2. Location and Nature of Practice Appropriate to PNP Use:

Eighty-six percent of the respondents agreed that PNP's might be best utilized in areas where health care is now inadequate, and it was generally considered that PNP's might provide a major solution to lack of pediatric care in such

areas. As pointed out earlier, however, only 3 percent of pediatricians characterized their practice as rural. Respondents to this questionnaire may therefore have been favoring PNP utilization in practice situations other than their own. In a similar paradox, 57 percent of solo pediatricians agreed that PNP's would best be utilized in large group practices, while 74 percent of those actually in the large groups disagreed with this statement.

3. Parental Acceptance:

Parental acceptance of the PNP was considered likely by 75 percent of pediatricians. Although 64 percent agreed that many mothers would rather talk to a PNP than to a pediatrician about certain problems, 58 percent felt that if given a choice a mother would always prefer to see a pediatrician, even if the child is healthy. A similar small majority (56 percent) expressed the belief that mothers would accept a PNP most readily in large group practice, though only 17 percent of the responding pediatricians practiced in large groups.

4. Quality of Care and Costs:

Fewer than one-third of the respondents agreed with statements that PNP's would lead to decreased quality of care. Only 15 percent believed that PNP's are a fad and would create more problems than they would solve. A majority (64 percent) predicted that utilizing PNP's would not decrease health care costs, in view of the expense of training and supervision.

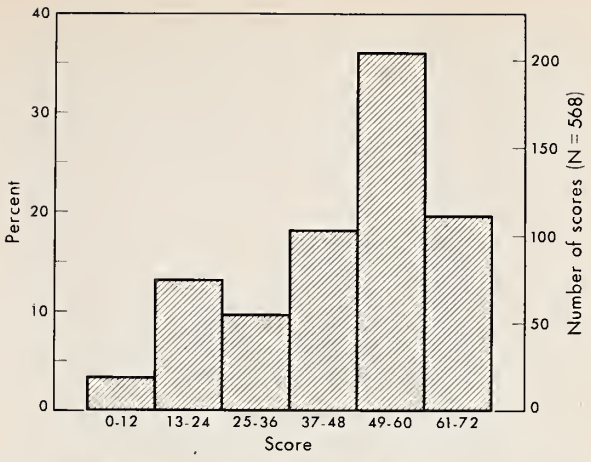


Chart 1.—Percentage distribution of scores representing expressions of attitude toward use of PNPs in pediatric practice by 568 California pediatricians.

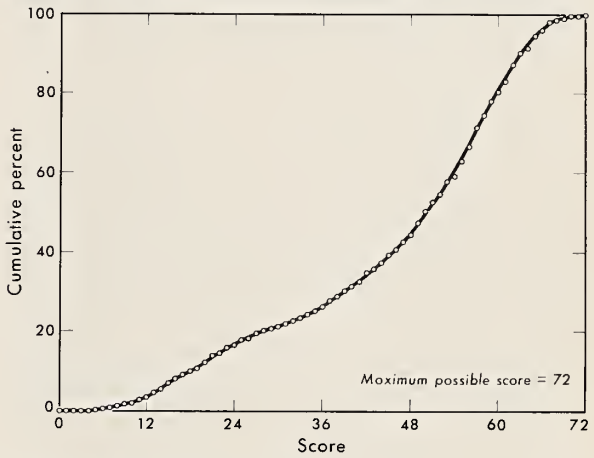


Chart 2.—Distribution curve of attitude scores represented in Chart 1.

Scoring

Respondents held generally favorable attitudes (questionnaire scores above the neutral level of 36) toward the concept of PNP practice with pediatricians. The over-all median score was 50; the mean score, 46. The percentage distribution of scores is shown in Chart 1. When numerical scores were plotted against cumulative percentages, the distribution for the 568 respondents was displayed as an "S" curve (Chart 2), indicating a broad and smoothly spread spectrum of opinion, with the curve skewed to the positive side.

When respondents were separated into four age groups (below 40 years, 40 to 49, 50 to 59, and 60 and over), those under age 50, the largest group of practicing pediatricians, appeared most favorable toward the utilization of PNP's in practice. Those in their 50s were less positive in their attitudes. The greatest percentage of negative responses was from physicians older than 60. The mean scores for the age groups were: below age 39, 48; ages 40 to 49, 48; ages 50 to 59, 42; over 60, 41. Similarly, the largest number of scores indicating a positive attitude toward use of PNP's came from those pediatricians who had been in practice less than 20 years, and the largest number of negative responses was from physicians who had been in practice more than 30 years.

A more important determinant of attitude than age and time in practice was the type of practice. Physicians in solo practice were least likely to view the PNP role favorably, although even they expressed a neutral rather than a negative attitude. Members of large groups and pediatri-

cians in the categories designated as "other" were most favorable to the PNP concept. Mean questionnaire scores were: solo practitioners, 38; two-pediatrician group, 42; three to five-pediatrician group, 43; large group, 55; "others," 56.

Individual Comments

Although no comments were solicited, 31 pediatricians wrote comments which varied from a few words to a two-page single-spaced letter, which generally expressed either strong agreement or strong disagreement with the PNP concept. Some were about current utilization of RN's or were words of caution for the future.

Strong agreement with the PNP concept came from pediatricians who have worked with or are interested in working with PNP's. It is significant that some pediatricians have apparently informally trained their own nurses in many of the tasks envisioned for the PNP.

Strong disagreement with the PNP concept was manifested by physicians who questioned the reality of the "manpower crisis," feared that the physician-patient personal relationship would deteriorate with the use of the PNP, wondered about the possibility of increased malpractice rates, and had concerns about the development of a "second-class M.D." Some recommended that more pediatricians, rather than PNP's, should be trained. A number of respondents expressed the opinion that PNP's would be useful, but not in their practices. Some solo practitioners suggested that PNP's might be used in large group practices, where relationships were said to be more impersonal; while a few group pediatricians considered that overworked solo practitioners would have the most need for PNP's.

A number of correspondents cautioned that the use of PNP's would increase the pediatrician's work load. It was pointed out that if a PNP takes over a major portion of the routine pediatric practice, the pediatrician will spend most of his time with sick patients, and will also be able to increase the total number of children under his care. He must then work longer hours, take more night and weekend calls (for which the PNP would be of no help), and would be subject to greater "nervous tension."

Discussion

Since those who responded to this questionnaire represent 53 percent of California pediatricians, it is obvious that only with caution can the views expressed be generalized to all pediatricians in this state. The percentage is large enough, however, that the opinions expressed merit serious consideration, and we offer these results as indicating the attitudes of those pediatricians who were sufficiently interested to answer a questionnaire mailed only once. Within these limits, the responses indicated that younger pediatricians tend to be engaged in group practice, and that most solo practitioners are in the later decades of life; this observation is in agreement with that of other observers.[1,2]

Our survey confirms findings in previous studies,[1,2] that pediatricians have a generally positive attitude toward the increased use of allied health personnel. Since pediatricians seem to like the idea of delegating certain aspects of their work to PNP's, one wonders why more PNP's are not employed in private practice.[13] Fewer than 12 of the 88 PNP's trained at the University of Colorado Medical Center since October 1965 were working with pediatricians in private practice as of January 14, 1972.[14] The great majority were in public health agencies or in teaching positions. Similarly, 90 percent of 256 California registered nurses delivering primary health care to children were working in public health agencies, schools, or other situations that differ considerably from private practice.[15] Eighty percent were directly responsible to non-physicians, such as other nurses, public health administrators, or school officials. The majority stated that they felt insecure about this and that they would prefer more physician guidance and communication.

The most important reason that there are so few PNP's in private practice may be a difference between the concepts of the PNP role held by pediatricians and by PNP's themselves. Our survey indicates that the pediatrician is willing to delegate certain tasks but hesitates to allow the PNP to function with much independence in direct patient care. This is in accord with office practice tradition: recent analyses[16,17] have shown that the nurse's role in the pediatric office is actually no different from that of a non-nurse office aide. Reservations expressed by respondents to the present questionnaire reflect this tradition. Some were concerned that an independent role for the PNP in office practice might lead to two levels of care.

Not all nurses interested in providing primary

care for children appear to want close physician supervision. Several recent articles suggest that nurses feel they can function more independently in well-child care; and that they aim to extend their role further into illness care.[18-22] Some PNP educational programs emphasize that they are training nurses in the extended role to act "not simply as physicians' assistants" but as independent and parallel professionals.[22]

Difficulties of another category may lead pediatricians to hesitate to employ PNP's. These include concern about a heavier and less well-balanced work load for the pediatrician. Some have predicted that the use of PNP's would eventually force the pediatrician to change the style, and even the location, of an established practice. Financial benefit from the use of the PNP in office practice depends upon the nature of the practice, the manner in which charges are made, and the number of patients scheduled for examination by the PNP. Although Schiff and coworkers[11] reported that after employment of a PNP income rose in a private two-pediatrician office, Charney and Kitzman,[23] in a more extensive and controlled study, could demonstrate no real cost benefit.

Any suggestion of a tendency to two levels of pediatric care must be avoided. Although most observers have indicated that patients accept PNP's well, Conant and associates[12] recently noted that lower middle-class and working-class patients do not accept care from allied health professionals as well as do upper middle-class patients. The shortage of health care for the nation's children is mainly among the poor. The needy must not be made to feel that the use of PNP's is another attempt to foist second-class care on them, while pediatricians and first-class care are reserved for upper-income patients.

If a pediatrician-PNP approach is to help solve the problems of pediatric care in this country, some pediatricians will need to develop a keener recognition of the degree of responsibility and independent action which PNP's can successfully assume. PNP educational programs will need to emphasize the practical team relationship of the PNP with the physician, with practicing pediatricians playing an important role in the training period.

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APPENDIX

Questionnaire Sent to 1150 Pediatricians

(1)_____A major solution to providing pediatric health care in areas and settings where such care is inadequate would be the utilization of PNA's.*

*The titles, "Pediatric Nurse Associate" (PNA), and "Pediatric Nurse Practitioner (PNP) are used interchangeably.[6]

(2)_____Extensive use of PNA's will adversely affect pediatric care because it will separate patient and physician.

(3)_____The success of a PNA in a practice will depend as much on the physician's acceptance of the PNA as on the patient's acceptance.

(4)_____Utilization of PNA's, even if not essential, could result in better health care for normal children.

(5)_____Most pediatricians spend too much of their time on well child care, and would like more time to spend on the ill child.

(6)_____Inasmuch as well child care is important, the pediatrician cannot afford to delegate it to another person.

(7)_____The PNA's primary usefulness is in a large group practice rather than in a private pediatric office (that is, with one or two pediatricians).

(8)_____Most mothers will not accept well child care provided by PNA's.

(9)_____Most pediatricians, in general, do not like the idea of utilizing PNA's in well child care.

(10)_____There may be some pediatric activities a PNA can perform more effectively than a pediatrician.

(11)_____If given a choice, a mother will always choose to see a pediatrician rather than a PNA, even if the child is healthy.

(12)_____The role of the PNA should be to supplement the pediatrician by seeing children for a portion of their regular visits, thus giving the pediatrician time to extend his care to more patients.

(13)_____The PNA, if utilized, should be under the constant observation of a pediatrician.

(14)_____The PNA would have greater acceptance among mothers attending a large group practice than among mothers visiting a solo practitioner in his office.

(15)_____The use of PNA's can only be considered a "fad" in providing health care rather than a more lasting solution.

(16)_____Eventually, the number of problems PNA's will create will be greater than the number of problems they will resolve.

(17)_____The utilization of PNA's will considerably reduce the costs of medical care.

(18)_____The role the PNA should be to replace the pediatrician in well child care.

(19)_____It is likely that the PNA will, on occasion, intrude on the pediatrician's area of specialization.

(20)_____The pediatrician's efforts should be directed to the treatment and care of patients rather than to the training of PNA's.

(21)_____Use of PNA's may lead to a reduction in the quality of medical care.

(22)_____The employment of PNA's leads to a reduction of the physician's medical responsibility to the patient.

(23)_____Considering the expense of training and supervising PNA's, there really will be no substantial decrease in medical costs.

(24)_____In reality, PNA's come close to practicing medicine and not nursing.

(25)_____The PNA would be likely to have greater acceptance among lower class mothers than among middle class mothers.

(26)_____Many mothers would feel freer to talk to a PNA about certain problems than they would with a pediatrician.

(27)_____The utilization of PNA's can only lead to enrichment and expansion for both professions.

(28)_____It would be advisable for nurses to focus on improving current nursing practices rather than extending themselves into other areas such as PNA.

(29)_____The presence of the PNA might eventually lead to deterioration of the doctor-patient relationship.

(30)_____The use of PNA's will eventually sacrifice quality of care for quantity (the number of patients cared for).

(31)_____Pediatricians should make more attempts to persuade retired nurses to return for training as PNA's.

(32)_____The PNA performs little more than the duties currently being performed by most pediatric office nurses.

(33)_____PNA's should perform only those activities the pediatrician cannot perform because of his time limitations.

(34)_____Many nurses and LVN's are likely to feel threatened by the presence of PNA's.

(35)_____It is conceivable that the future role of the PNA could include the treatment of children with minor abnormalities and/or illness.

(36)_____At present, PNA programs are being sponsored and pushed by a well organized minority of pediatricians.

(37)_____Many mothers would prefer to see a pediatrician rather than a PNA since they might be afraid the PNA would not pick up some abnormalities.

(38)_____Please rate the following items as to their relative importance to the mother upon her visit to your office by placing one of the following appropriate numbers in the blank space provided in front of the item.

1 VERY IMPORTANT
2 MODERATLY IMPORTANT
3 MODERATELY UNIMPORTANT
4 VERY UNIMPORTANT

(a)_____A thorough physical examination

(b)_____Interest shown in the child

(c)_____Advice or information on child rearing

(d)_____Reassurance of the child's normal dvelopment

(e)_____Full and clear explanations

(f)_____A sympathetic and understanding pediatrician

Your age:_____years Sex:_____Male _____Female

Length of time in practice as a pediatrician:_____years

Type of practice (check one):

() Solo () Small Group (2 or less pediatricians)

() Medium Group (3 to 5 pediatricians)

() Large Group (6 or more pediatricians)

() Other (please specify)_____

Location of practice:

() Urban () Rural () Suburban

Are you a member of the American Academy of Pediatrics? _____yes _____no

Refer to: Beall GN, O'Toole J, Katz E, et al: A survey of the resources for the teaching of clinical allergy in California (Information). Calif Med 118:69-72, Jan 1973

Information

A Survey of the Resources for The Teaching of Clinical Allergy in California

GILDON N. BEALL., M.D., *Torrance*, JOHN O'TOOLE, M.D., *Riverside*,
EDWARD KATZ, M.D., *Beverly Hills*, AND MILTON MILLMAN, M.D., *San Francisco*

RECENT EVENTS ENLARGING the scientific base of clinical allergy have re-awakened interest in this subject. The interest is timely since there has been no notable decrease in the large numbers of patients afflicted with allergic disorders. Unfortunately, many physicians now in practice have completed their formal medical education with little or no experience in clinical allergy. Consequently, it seemed appropriate to learn what resources for continuing medical education in clinical allergy existed in California.

As with most chronic illnesses, learning about allergic diseases is facilitated by exposure to patients over a relatively long time. Since these patients are usually ambulatory, it seemed likely that outpatient allergy clinics in the various hospitals in California would be the most likely setting to provide this experience. In this paper we will present some results of a survey of these clinics.

Methods

The membership of the California Society of Allergy and California members of the American Academy of Allergy were surveyed as to their participation in any formal allergy clinics which were taking part in teaching or could do so. By this means, the names of the clinic directors were found and a detailed follow-up survey was sent to those directors. Forty clinics were listed.

All but two or three of these clinics expressed belief that they can offer useful training to practicing physicians and almost as large a number believe they can offer useful experience to those who are already acting as specialists in allergy. Information on the meeting times, numbers and types of patients seen and other details about the clinics can be obtained from the Clinic Directors or from the Advisory Panel on Allergy to the California Medical Association, 693 Sutter Street, San Francisco 94102.

List of Allergy Clinics in California Engaged in or Capable of Conducting Teaching Programs

Fresno
Valley Medical Center of Fresno
445 South Cedar Avenue 93702
Samuel Ross, M.D.—Adult Allergy Clinic
John P. Conrad, M.D. and William Ziering, M.D.—Pediatric Allergy Clinic

La Jolla
Scripps Clinic and Research Foundation
476 Prospect Street 92037
E. Tan, M.D. and J. Vaughan, M.D.—Adult Allergy Clinic

Long Beach
Long Beach Veterans Administration Hospital
5901 E. 7th Street 90801
Kent Thayer, M.D.—Adult Allergy Clinic

This report was given by a Study Group of the Advisory Panel to the California Medical Association Section on Allergy at the meeting of April 21, 1972, and approved for publication.

Reprint requests to: G. N. Beall, M.D., Harbor General Hospital, 1000 W. Carson Street, Torrance, Ca. 90509.

Los Angeles
Cedars of Lebanon Hospital
4833 Fountain Ave. 90024
Ron Reuben, M.D.—Pediatric Allergy Clinic

Los Angeles
Children's Hospital of Los Angeles
4650 Sunset Blvd. 90027
Warren Richards, M.D.—Pediatric Allergy Clinic

Los Angeles
Good Hope Clinic—Good Samaritan Hospital
1227 Wilshire Blvd. 90017
Ralph Bookman, M.D.—Adult Allergy Clinic

Los Angeles
Queen of Angels Clinic
2301 Bellevue 90026
Ralph Bookman, M.D.—Combined Pediatric and Adult Allergy Clinic

Los Angeles
UC, LA, Medical Center
405 Hilgard Ave. 90024
R. Robinett, M.D. and G. Beall, M.D.—Adult Allergy Clinic
Sheldon C. Siegel, M.D., and Richard Stiehm, M.D.—Pediatric Allergy Clinic

Los Angeles
Los Angeles County-USC Medical Center
1200 No. State Street 90033
Walter R. MacLaren, M.D.—Adult Allergy Clinic
Zack H. Haddad, M.D.—Pediatric Allergy Clinic (Pediatric Pavilion)

Los Angeles
White Memorial Medical Center
414 N. Boyle Avenue 90033
E. Swerdloff, M.D.—Combined Pediatric and Adult Allergy Clinic

Oakland
Oakland Naval Hospital
8750 Mountain Blvd. 94627
Richard Barrick, M.D.—Adult Allergy Clinic

Orange
Children's Hospital of Orange County
1109 W. La Veta Ave. 92668
Leo H. Cummins, M.D.—Pediatric Allergy Clinic

Orange
Orange County Medical Center, UC, Irvine
101 Manchester Ave. 92668
Harold S. Novey, M.D.—Adult Allergy Clinic
Thomas L. Nelson, M.D. and Stanley Galant, M.D.—Pediatric Allergy Clinic

Palo Alto
Children's Hospital at Stanford
520 Willow Rd. 94304
V. A. Marinkovich, M.D. and M. Yamate, M.D.—Pediatric Allergy Clinic

Pasadena
Huntington Hospital
Pasadena Dispensary
38 Congress Street 91105
Walter MacLaren, M.D.—Combined Pediatric and Adult Allergy Clinic

Sacramento
Sacramento Medical Center, UC, Davis
2315 Stockton Blvd. 95817
N. Whitcomb, M.D. and J. Garland Stroup, M.D.—Pediatric Allergy Clinic

Sacramento
David Grant Medical Center
Travis Air Force Base, Fairfield 94535
Ned Whitcomb, M.D.—Combined Pediatric and Adult Allergy Clinic

Salinas
General Hospital of Monterey County
1330 Natividad Road 93901
D. Stofer, M.D.—Combined Pediatric and Adult Allergy Clinic

San Bernardino
San Bernardino County General Hospital
780 E. Gilbert St. 92404
D. Gorenberg, M.D.—Combined Pediatric and Adult Allergy Clinic

San Diego
Mercy Hospital and Medical Center
4077 Fifth Ave. 92103
Milan Brandon, M.D. and John J. Stevens, M.D.—Combined Adult and Pediatric Allergy Clinic

San Diego
University Hospital of San Diego County
225 W. Dickinson St. 92103
James P. Kemp, M.D. and Robert Hamburger, M.D.—Pediatric Allergy Clinic

San Francisco
Children's Hospital and Adult Medical Center
3700 California St. 94118
William C. Sawyer, M.D.—Adult Allergy Clinic

San Francisco
Kaiser Hospital
2200 O'Farrell St. 94115
B. Feingold, M.D.—Combined Pediatric and Adult Allergy Clinic

San Francisco
Letterman General Hospital
Presidio of San Francisco 94129
J. L. McGerity, M.D.
Adult Allergy Service

San Francisco
Mt. Zion Hospital and Medical Center
1600 Divisadero St. 94115
William C. Sawyer, M.D.
Combined Pediatric and Adult Allergy Clinic

San Francisco
St. Luke's Hospital
3555 Army St. 94110
S. Scarlett, M.D.
Combined Pediatric and Adult Clinic

San Francisco
St. Mary's Hospital and Medical Center
Stanyon & Hayes Streets 94117
William C. Sawyer, M.D.
Combined Pediatric and Adult Allergy Clinic

San Francisco
San Francisco Children's Hospital
3700 California St. 94118
Herbert S. Kaufman, M.D.
Combined Pediatric and Adult Allergy Clinic

San Francisco
San Francisco General Hospital
22nd and Potrero 94110
W. Deamer, M.D. and O. L. Frick, M.D.
Pediatric Allergy Clinic

San Francisco
University of California Medical Center of San Francisco
3rd and Parnassus 94122
W. Epstein, M.D.
Adult Allergy Clinic

San Jose
Santa Clara Valley Medical Center
Bascom and Moorpark Ave. 95128
W. R. Starr, M.D.
Adult Allergy Clinic

San Mateo
San Mateo County General Hospital
222 W. 39th Ave. 94403
L. Melcher, M.D.
Adult Allergy Clinic

Santa Barbara
Santa Barbara General Hospital
300 San Antonio Rd. 93105
H. Styler, M.D.
Combined Pediatric and Adult Allergy Clinic

Santa Monica
Santa Monica Hospital & Medical Center
1255 Fifteenth St. 90404
Leon Harris, M.D.
Combined Pediatric and Adult Allergy Clinic

Torrance
Harbor General Hospital
1000 West Carson St. 90509
Gildon N. Beall, M.D.—Adult Allergy Clinic
Douglas C. Heiner, M.D.—Pediatric Allergy Clinic

A number of the clinics listed are associated with medical schools or their affiliated hospitals. In general, these clinics are already active in teaching house staff, medical students and, in some cases, physicians in practice. In contrast, the teaching resources of some other clinics seem to be under-utilized.

A possible additional resource that we have not listed is the private offices and patients of practicing allergists.

At many of the institutions there are regular didactic conferences at which subjects of allergic and immunologic importance are discussed. Most of the respondents indicated that these conferences were open to all interested physicians.

List of Didactic Conferences on Subjects of Allergic and Immunologic Importance

La Jolla
Scripps Clinic & Research Foundation
Combined Clinical Immunology Conference
Tuesday—12:30-1:30 p.m.
Allergy Clinical Conference
Thursday—12:30-1:30 p.m.

Loma Linda
Loma Linda University Hospital
Pulmonary and Infectious Disease Conference
Wednesday—12:00-1:00 p.m.

Los Angeles
Children's Hospital of Los Angeles
Allergy Conference
Tuesday—10:30 a.m.

Los Angeles
UC, LA, Pediatric Allergy Clinic
Allergy/Immunology Seminar
Thursday—8:00-12:00 p.m.

Los Angeles
Los Angeles County-USC Medical Center
Pediatric Allergy/Immunology
Thursday—11:30-12:30 p.m.
Immunology Sessions
Friday—1:30-2:30 p.m.

Orange
Orange County Medical Center
Combined Adult/Pediatric Rounds
Wednesday—11:00-Noon; and Friday—10.30-Noon

Palo Alto
Children's Hospital at Stanford
Allergy/Immunology Journal Club
Thursday—Noon

Salinas
General Hospital of Monterey County
Allergy Conference
Wednesday—9:00 a.m.

San Diego
University Hospital
Allergy Rounds
Tuesday—Noon
Joint Seminar with San Diego Allergy Society
Third Wednesday—7:30 p.m.

San Francisco
Children's Hospital & Adult Medical Center
Allergy/Immunology Conference
Twice Monthly

San Francisco
Letterman General Hospital
Internal Medicine Rounds
First Wednesday of the month—9:30-11:00 a.m.
Allergy & Chest Service Conference
First Thursday of the month—11:00-12:00
Pediatric Allergy Rounds
Last Thursday of the month—3:30-5:00 p.m.

Torrance
Harbor General Hospital
Immunology Discussion Group
Wednesday—12:00-1:00
Pediatric Allergy/Immunology Seminar
Wednesday—8:00-9:00 a.m.

Walnut Creek
Permanente Medical Group
Allergy Conference
Wednesday—9:00-10:00 a.m.

(Specific details about times and places of meetings should be obtained from the institutions.)

Formal postgraduate courses with one to three day lecture formats are offered periodically by many of the medical schools and hospitals. Those courses are usually well publicized by direct mailings as well as announcements in CALIFORNIA MEDICINE and other periodicals.

It is apparent that there are many resources for continuing medical education in clinical allergy in California. Since we have received many comments indicating that these resources are under-utilized, we hope that publication of this information will stimulate interest in continuing medical education in allergy.

CLINICAL CARDIOLOGY SERIES

The Syndrome of Midsystolic Extra Sound And Late Systolic Murmur

WILLIAM E. SHELL, M.D.

Material Supplied by the American Heart Association

MID-LATE SYSTOLIC CLICKS AND THE ASSOCIATED late systolic murmurs are frequently encountered in clinical practice. Concepts concerning the

The author is from the Department of Medicine, University of California, San Diego, School of Medicine, La Jolla.

generation of these auscultatory phenomena have undergone rapid evolution in the last ten years. Traditionally, these sounds were considered to be benign extracardiac events generated by the motion of pleural-pericardial adhesions. However, it is now established that they are related to mild mitral regurgitation and emanate from tension on a large ballooning, redundant posterior mitral valve leaflet. Moreover, in a substantial proportion of cases, there is a strong familial association of mid-late systolic extrasounds and late systolic murmurs indicating a congenital cause for the valvular abnormality.

Auscultation

The mid-late systolic extrasound or click is a high pitched transient, usually best heard at the apex but often radiating widely. The most salient feature is its extreme variability. The sound may vary with position and/or respiration in an unpredictable fashion. Its quality, intensity, and position in the cardiac cycle can vary from moment to moment without provocation. In certain patients the sound is appreciated only in the standing positions, while in others, only in the left lateral or the supine position. Thus, careful auscultation will be necessary to detect its presence. Frequently, there is an associated systolic murmur of mitral regurgitation. In most instances the murmur will be confined to late systole and follow the systolic click. However, pansystolic and midsystolic murmurs also occur with the systolic extrasound and also indicate mitral regurgitation. The murmur also is variable, but to a lesser degree than the sound. It may be high pitched and is frequently located at the apex, with poor radiation. The murmur, as well as the sound, may be difficult to hear, and again careful auscultation is necessary.

Cineangiocardiography

The cineangiocardiograms in the majority of patients with either systolic extrasounds or late systolic murmurs show a peculiar retroversion of the posterior mitral leaflet during mid to late systole. The valve leaflet balloons backward like a sail caught in a strong wind and fills with contrast medium. The systolic extrasound occurs at the height of the excursion of this redundant leaflet. The floppy valve can be easily seen in either oblique position. Frequently, there is a mild degree of mitral regurgitation usually confined to late systole.

Pathologic Studies

There have been few postmortem examinations reported in patients with these auscultatory phenomena. Barlow reported a man who died suddenly and who had enlarged redundant posterior leaflet with normal chordae tendineae. We have examined the valves of two patients with midsystolic extrasounds, late systolic murmurs, and abnormal cineangiocardiograms. The findings were similar in both patients. The anterior leaflet area was 2 to 4 times larger than normal, while that of the posterior leaflet was 4 to 6 times greater than expected. Both patients had extensive deposition of a sulfated mucopolysaccharide in the media of the valve leaflets while the chordae tendineae, as well as the coronary arteries, were normal.

Clinical Syndrome

The majority of patients with either midsystolic extrasounds or late systolic murmurs are asymptomatic and the auscultatory phenomena are found incidentally. Two major symptom complexes merit discussion. Many of the patients complain of chest pain. The pain is substernal and crushing in quality. It is brought on by exercise but may occur at rest. It lasts minutes to hours and is poorly responsive to nitroglycerin. The pain has been attributed to angina pectoris, coronary insufficiency, myocardial infarction, and noncoronary chest pain, depending on which components are most prominent in a particular patient. Coronary arteriograms have been normal in patients studied. The bouts of prolonged chest pain rarely are accompanied by enzyme rises. In a recent study of young females with chest pain, positive exercise tests and normal coronary arteries, 4 percent had the midsystolic click-late systolic murmur syndrome. The exact cause of the chest pain is obscure.

These patients frequently complain of palpitations. Several types of arrhythmia have been documented, including premature ventricular contractions, exercise-induced ventricular tachycardia, paroxysmal atrial fibrillation, and paroxysmal atrial tachycardia. The cause is not entirely clear. Sudden death may occur in patients with the syndrome and among their first degree relatives.

Electrocardiograms

Electrocardiograms are frequently abnormal in patients with late systolic murmurs and/or mid

late systolic extrasounds. The abnormalities consist of T-wave flattening and inversion in leads II, III, avf, V_{4-6}. Evidence of transmural myocardial infarction is seen rarely. Exercise electrocardiograms in patients with chest pain and auscultatory evidence of floppy valves are frequently positive exhibiting ST segment depression despite normal coronary arteriograms. Exercise testing may precipitate arrhythmias, including multiple premature ventricular contractions and ventricular tachycardia. Thus, such tests in patients with the ballooning mitral valve syndrome should be performed with caution and careful monitoring.

Diagnostic Studies

A number of noninvasive tests may be used to establish the origin of the late systolic murmur as mitral regurgitation. Amyl nitrite administration causes the mid-late systolic extrasound to move earlier in systole frequently merging with the first heart sound. The late systolic murmur also moves earlier in systole and may become pansystolic; its intensity does not change.

Handgrip may be very effective in evaluating these auscultatory phenomena. Handgrip may bring out a systolic extrasound which is evanescent and difficult to document.

Ultrasound examination of the mitral valve often is characteristic in the syndrome. Abnormal motion of the anterior leaflet as well as clear separation of the leaflets on the echogram are common. When present, these signs are nearly pathognomic of the ballooning posterior leaflet syndrome.

A majority of patients with either midsystolic extrasounds or late systolic murmurs are asymptomatic. Their prognosis for longevity appears independent of the extent of abnormality in the mitral leaflets. However, the occurrence of chest pain and arrhythmias is associated with considerable prognostic uncertainty. The rate of progression of the mitral regurgitation is unknown. Thus, asymptomatic patients with the auscultatory phenomena of the syndrome must be followed periodically.

When chest pain is prominent, treatment with propranolol and long-acting nitrates may be initiated. This mode of therapy has afforded significant relief in some patients. Control of arrhythmias is indicated in light of the incidence of sudden death. Ventricular extra systoles should be treated with propranolol and digitalis, while atrial arrhythmias can often be managed effectively with digitalis alone.

CLINICAL CARDIOLOGY SERIES

Treatment of Cardiogenic Shock

Part 1

LAWRENCE S. COHEN, M.D.

Material Supplied by the American Heart Association

ALTHOUGH THE TREATMENT of cardiac arrythmias following a myocardial infarction has decreased in-hospital mortality, cardiogenic shock remains a major cause of death. The mortality rate of cardiogenic shock is still in the range of 75 to 80 percent. It is estimated that more than 100,000 persons die yearly in the United States with this syndrome. The clinical profile of the patient with cardiogenic shock is familiar. At some point after a heart attack the blood pressure starts to fall and is usually no greater than 80 mm of mercury systolic. Tachycardia, 120 to 140 beats per minute, is quite usual. The skin color is a dusky cyanotic gray and the patient is markedly diaphoretic. Urine output falls and the patient's sensorium becomes clouded. He will often be barely arousable or may be quite irrational. Terminally, ventricular tachyarrhythmias or heart block may occur.

If any one form of therapy had proved to be successful there would be little controversy concerning the proper medical therapy for this condition. Since the mortality is so high, many forms of therapy have been advocated. In the absence of uniform agreement concerning therapy the following approach is one which the author accepts as a generally reasonable one. It

This article is to be published in two parts. Part II will appear in a subsequent issue.

Dr. Cohen is from Yale University School of Medicine, New Haven.

is axiomatic that therapy must be individualized for each patient and that no patient should receive a predetermined regimen.

The principles of therapy for cardiogenic shock follow from the pathophysiology of this condition. There is increasing evidence that the major factor leading to cardiogenic shock is an inability of the left ventricle to perform adequately as an effective pump. In almost all cases cardiac output is markedly diminished. Similarly, the hypotension which is a hallmark of this syndrome is in large part a consequence of low cardiac output. Since a critical pressure is necessary to maintain coronary filling, the hypotension has deleterious effects upon coronary filling and this in turn leads to further deterioration in the ability of the heart to support the circulation.

The two goals of therapy for this condition are (1) to increase the cardiac output and (2) to raise systemic blood pressure. Both of these goals could be achieved if the left ventricle were helped sufficiently to augment its contractility.

General Considerations

Since cardiogenic shock has such a dreadful prognosis, any patient with this syndrome should be treated in a specialized facility capable of handling the intricate problems that arise. Adequate bedside and central nursing station electrocardiographic monitoring should be available. An intravenous line capable of measuring central venous pressure should be present and fluids and medication may be administered through it. Although it is desirable in certain circumstances to be able to directly record arterial pressure through the use of a strain gauge and pressure transducer, this latter intervention is not absolutely essential.

The measurement of central venous pressure may be important in unmasking hypovolemia as a contributory factor to the shock. With the widespread use of diuretics in cardiac patients it is not unusual for the patient who sustains a myocardial infarction to have the problems of hypovolemia added to those of pump failure. Although it is well recognized that the central venous pressure may be totally normal, even if the patient is in pulmonary edema, knowledge of the central venous pressure does help management. If the central venous pressure is low or normal and if the patient is not in gross left sided congestive heart failure with rales, dyspnea and roentgenographic evidence of pulmonary edema, judicious fluid therapy may be extremely valuable in reversing the state of circulatory failure. By taking advantage of the fact that as left ventricular end diastolic pressure and volume increase, so will left ventricular work and stroke output, a trial of 250 ml of isotonic saline solution or low molecular weight dextran may be tried. If this improves the circulatory state, then another 250 ml may be given. At times a simple therapeutic maneuver such as fluid administration may be of great help in relieving many of the manifestations of this syndrome.

If central venous pressure is elevated in the absence of cor pulmonale, there is generally little chance that fluid administration will be helpful and the danger of causing pulmonary edema increases.

Other general principles such as oxygen administration and adequate pain relief will not be commented upon here, other than to mention them. Pain, such as that which may occur with a myocardial infarction, may often lead to vagal reflexes which potentiate hypotension. Sufficient analgesia should be given to alleviate pain completely.

Digitalis Glycosides

There is considerable controversy concerning the role of digitalis glycosides in the syndrome of cardiogenic shock. The argument usually cited by physicians who are reluctant to utilize digitalis is the recognized potential of digitalis to cause ventricular arrhythmias. More recently, it has been shown that any intervention which increases the velocity of myocardial contraction also increases myocardial oxygen consumption. One of the actions of digitalis is to raise the velocity of contraction and therefore it may raise myocardial oxygen consumption. It has been demonstrated that areas of myocardium which are marginally oxygenated following an occlusion of a coronary artery may become necrotic instead of ischemic if myocardial oxygen consumption is augmented. However, if one accepts the thesis that the primary abnormality in cardiogenic shock is a marked depression of left ventricular contractility, then digitalis therapy becomes a very rational means of trying to restore circulatory integrity. Unfortunately a controlled study of digitalis therapy in cardiogenic shock is still not available.

It is the author's practice to administer digitalis early in the course of cardiogenic shock if the patient is not already taking this medication. The onset of action and peak effect of intravenous digoxin are such as to make it a perfectly reasonable drug to use. Between 1.0 and 1.5 mg of digoxin is given intravenously in approximately a two-hour period in doses of 0.25 mg every 15 or 20 minutes.

It should be noted that pulmonary venous congestion or other signs of left heart failure need not be present in a patient with cardiogenic shock. The author feels, nonetheless, that digitalis plays a role in the therapy of the patient in cardiogenic shock. It should be recognized, however, that this form of therapy is not agreed upon uniformly.

Vasopressors

The most easily recognizable feature of cardiogenic shock is hypotension. A variety of agents are available to raise arterial blood pressure. The sympathomimetic amines have been given considerable use. These drugs have been classified into alpha or beta stimulatory agents. Alpha adrenergic drugs act primarily on the peripheral arterioles and raise blood pressure by increasing peripheral resistance. Included in this group are methoxamine (Vasoxyl) and phenylephrine (Neo-synephrine). A second category of drug not only stimulates alpha adrenergic receptors in the peripheral arterioles but also stimulates beta adrenergic receptors in the myocardium. Metaraminol (Aramine®), nor-epinephrine (Levophed®) and epinephrine are examples of this type of agent. An example of a sympathomimetic amine which has only beta stimulating effects is isoproterenol (Isuprel®). Since isoproterenol acts as a peripheral vasodilator it does not appropriately fall into the category of a vasopressor, although it is a sympathomimetic amine.

Although raising the blood pressure is generally considered an appropriate goal in the treatment of a patient in cardiogenic shock, the issue is not quite that simple. Since most filling of the coronary arteries occurs in diastole, the coronary arteries do require a certain level of pressure in the central aorta in order to fill. Myocardial function is dependent upon adequate coronary blood-flow and will deteriorate in the presence of inadequate perfusion pressure.

It has been shown, however, that drugs which act only on the peripheral arterioles, thereby raising blood pressure by elevating peripheral vascular resistance, may have a deleterious effect upon patients in cardiogenic shock. If left ventricular function is sufficiently impaired to place a patient into cardiogenic shock, increasing the resistance against which the left ventricle must pump may further decrease cardiac output.

For this reason, drugs which act solely on the peripheral vasculature, such as methoxamine or phenylephrine, have little or no role in the therapy of cardiogenic shock.

Agents which act both on the beta receptors of the myocardium and the alpha receptors of the periphery have been used most extensively. It is wise to use no more of these agents than is necessary to maintain an adequate perfusion pressure and it is also advisable to give them by intravenous drip rather than intramuscularly, for blood pressure then can be titrated more precisely. It is not necessary for the blood pressure to be brought to normal levels. A systolic blood pressure of 90 to 100 mm of mercury is usually adequate. It is the author's practice to place 50 mg of metaraminol in 500 ml of 5 percent dextrose in water. This is infused at a rate sufficient to elevate blood pressure the desired amount.

Nor-epinephrine (Levophed) is another sympathomimetic amine which has potent effects upon both the peripheral and the central circulation. Although blood pressure can generally be raised by an intravenous drip of nor-epinephrine, experience indicates that relatively few patients survive if it becomes necessary to use this drug in order to sustain blood pressure.

Glucagon

Glucagon, a hormone which has been shown to raise blood sugar has also been utilized recently in patients with cardiogenic shock. Although its mechanism of action is not known precisely, it does have the property of increasing cardiac contractility, possibly by augmenting the synthesis of cyclic AMP. Initial studies of this agent in the animal laboratory and in the human cardiac catheterization laboratory led to some enthusiasm for its use in patients with myocardial infarction and shock. Other than for some anecdotal reports of its efficacy, this agent has generally been disappointing in the treatment of this condition and has generally been abandoned as a therapeutic agent.

PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Director, State Department of Public Health

Safe Medical Devices

MEDICAL DEVICES ARE an important part of every physician's diagnostic and therapeutic equipment, from the stethoscope, sphygmomanometer and clinical thermometer to the pressure transducer and heart-lung machine.

The State Department of Public Health, Bureau of Food and Drug, has the responsibility of assuring the safety and efficacy of all devices intended for use in the diagnosis, cure or treatment of disease, or intended to affect any structure or function of the human body. In California they must be manufactured on licensed premises, and good manufacturing practices must prevail in such establishments. Labeling should indicate whether the device is intended for investigational use only or may be used for treatment and, if so, whether medical supervision is required. Directions, description of hazards, and warnings must be provided unless they are commonly known. For a new device which is not generally recognized among qualified experts as safe and effective for use, clearance must be obtained before it may be sold.

The Department is currently interested in learning of any defective or improperly constructed medical devices so that hazards to patient and doctor and allied medical personnel may be eliminated. Deaths have been reported to us recently from explosions of dental gas installations; also instances of improperly controlling heating units in incubators; electrical shocks from physiotherapy equipment; improperly insulated dialysis equipment; dialysis membranes with a high rupture rate; ventilators which vary with voltage changes and spontaneously fail; and pacemakers with short life expectancies.

The Department is currently licensing California device manufacturers whose manufacturing facilities are adequate and whose products are made under good manufacturing practices. We suggest that physicians and hospitals inquire whether their California-manufactured devices come from sources licensed by this Department and that we be notified of any unlicensed manufacturers of medical devices in this state that may come to your attention. We are also interested in learning of any instance of medical equipment failure or inadequate performance since problems with medical devices involve not only their condition at time of sale or installation, but also the effects of time and continued use. We urge every institution with medical equipment to implement a preventive maintenance and inspection program to make sure that equipment in current use is performing safely and effectively at all times, and that fail-safe mechanisms or back-up equipment are readily available in the event of component or instrument failure. A competent medical equipment safety engineer can provide invaluable services in protecting the health of patients.

application for HOTEL ACCOMMODATIONS

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And
Second Invitational Western States Scientific Assembly

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HOUSE OF DELEGATES OPENING SESSION **SATURDAY AFTERNOON, MARCH 10**

1. Fill in the form below *completely* for room accommodations at the CMA's 1973 Annual Session. There are only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations, except for suites, must be made through the Disneyland Hotel, 1441 S. West Street, Anaheim, California 92802, by February 9, 1973.
4. ALL SUITE RESERVATIONS MUST BE CLEARED THROUGH THE CMA CONVENTION OFFICE, SAN FRANCISCO. *IF YOU ARE REQUESTING A SUITE, DIRECT YOUR REQUESTS TO: CMA CONVENTION OFFICE, 693 SUTTER STREET, SAN FRANCISCO, CA. 94102.*
5. CANCELLATIONS: Please notify Disneyland Hotel, 1441 S. West Street, Anaheim, of all cancellations. CHANGES: All other changes to be made directly with hotel at all times.
6. FIRST NIGHT DEPOSIT: PLEASE ENCLOSE THE FIRST NIGHT'S RENTAL AS DEPOSIT. REFUNDABLE ONLY IF HOTEL IS NOTIFIED 5 DAYS BEFORE ARRIVAL DATE.

DISNEYLAND HOTEL

	Standard	Deluxe
Singles	$ 20.00	$ 26.00–30.00
Twins or doubles	24.00	28.00–32.00
Additional person in room	4.00	4.00
1 Bedroom suites		65.00–75.00–85.00
2 Bedroom suites		100.00–110.00

SEND TO: DISNEYLAND HOTEL RESERVATIONS
1441 S. West Street, Anaheim, California 92802

Please reserve the following accommodations for the CMA's 1973 Annual Session in Anaheim, March 10-14.

Single Bedroom $.....Twin-Bedded $.....Double Bed $.....Suite $.....

Arrival (date) Hour a.m. / p.m. Departure (date) Hour a.m. / p.m.

THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: Officer?..... Delegate? Alternate?..... Speaker?

Address: County

City and State Zip Code

GUESTS' NAMES AND ADDRESSES:

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.....

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

APPROACH TO THE MEDICAL CARE OF THE SICK NEWBORN—Sophie H. Pierog, M.D., Physician in Charge of Nursery Services and the Birth Defects Program, Jewish Hospital and Medical Center of Brooklyn, Clinical Assistant Professor, Department of Pediatrics, State University of New York, Brooklyn, Lecturer, New York Hospital-Cornell Medical Center, Institutes in the Care of Premature and Other High Risk Infants; Angelo Ferrara, Associate Professor in Clinical Pediatrics, New York University School of Medicine, New York, Director of Newborn Transport Services, The City of New York, Lecturer, New York Hospital-Cornell Medical Center, Institutes in the Care of Premature and Other High Risk Infants. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1971. 292 pages, $11.50.

This compact little book contains a great deal of information making it a useful addition to any nursery. It would be particularly valuable to house staff, medical students and nurses. It has an excellent section on diagnosis and management of abnormal signs and symptoms in newborn infants and is well referenced, with the exception of the chapter on hematologic considerations which has none.

It would be of less use to hospital administrators for whom it was also written. The chapter on organization of newborn services is wordy rather than informative, and the useful list of equipment and manufacturers is so incomplete as to be confusing. There are, for example, fourteen oxygen analyzers on the market. The authors list only two. It would also have been nice if the authors could have told us the advantages and disadvantages of various monitors and analyzers. This much-needed information is quite unavailable at the present time. The reader does not know where to buy exchange transfusion sets, phototherapy equipment or transillumination lights but the text says these are important.

There are a few errors and omissions. For example, perinatal mortality is quoted as 270 per 1000 live births at term, instead of 27; umbilical arterial saturation is quoted as 0.51 percent instead of 20 percent; normal blood pressure is said to be $\frac{7}{50}$ mmHg ± 10, instead of $\frac{70}{50} \pm 10$. The management of meconium staining with meconium aspiration in resuscitation of the newborn is omitted for some reason and yet this may occur in 10 percent of deliveries. The complications of pneumothorax and pneumomediastinum are not stressed or discussed.

There is a useful section on parental education and counselling. The appendices of procedures, drugs and laboratory values are brief and helpful.

I believe the strength of this book as a quick diagnostic guide is greater than its value as a comprehensive therapeutic or administrative manual. However it should have a place on the shelves on any busy nursery.

JUNE BRADY, M.D.

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DARWIN'S VICTORIAN MALADY—Evidence for Its Medically Induced Origin—John H. Winslow, Department of Geography-Anthropology, California State College (now Department of Geography, University of Papua and New Guinea). American Philosophical Society, Independence Square, Philadelphia (19107), 1971. 94 pages, no price listed.

For generations physicians have taught and have been taught to exercise caution in making "snap" diagnoses on their patients from hearsay evidence or the clinical history alone without a thorough physical and, where necessary, laboratory examination. Besides, at the court of last appeal —the postmortem—extensive microscopic, bacteriological, and biochemical tests are necessary and even then uncertain and contradictory conclusions may be expressed. However, these wise rules fortunately, and often unfortunately, do not apply to the "paper" diagnosis and postmortem so often made on historical figures.

In the last two or three decades the favorite subject for such historical appraisals has been Charles Darwin whose lengthy and long publicized illness, abundantly documented with hearsay and unscientific evidence, has made him the target of highly speculative opinions, both amateur and professional, as to its cause. The spate of such opinions has recently centered primarily around a dispute as to whether Darwin's long illness was a neurosis with psychosomatic manifestations or whether he had acquired Chagas' disease on his South American visit.

The present excursion into Darwin's chronic state of ill health is presented by a geographer whose thesis is that all of Darwin's ailments can be traced to chronic arsenic poisoning iatrogenically or self-induced from the excessive and improper use of Fowler's solution employed as a tonic and for the treatment of "eczema" during his student days. Thereafter, in support of this thesis, the author's method is to list every recorded symptom from around the period of Darwin's voyage on *H.M.S. Beagle* to the time of his death and adduce documentary evidence that comparable symptoms occur in chronic arsenic poisoning. He seeks further support of his thesis from the frequency with which Fowler's solution was employed in the therapy of the period. From this he further asserts that Darwin and his many contemporaries classed as "dyspeptics" or "hypochondriacs" such as De Quincy, the Thomas Carlyles, Robert Browning, George Lewes, Margaret Ossoli, Herbert Spencer, Thomas Henry Huxley and George Eliot were in fact suffering from "Fowler's Disease" or chronic arsenical poisoning medically induced.

The arsenic theory to account for Darwin's invalidism is not new. It was discussed by Lawrence Kohn, Clinical Professor of Medicine at Rochester, some ten years ago only to be peremptorily dismissed as "far fetched"—an opinion which the present memoir does little to disturb. The trouble with the author's thesis is that it suffers from what can only be designated as symptomatological "overkill." It is not that chronic arsenical poisoning with its protean manifestations may have been a possible factor in Darwin's illness, but the problem is one of carefully weighing the symptomatology in chronological sequence to support such a diagnosis as even probable. Instead we are asked to swallow one questionable assumption after another in the lumping together of symptoms and methods of therapy, all of which serves to emphasize that the author has had no experience with arsenical poisoning whatsoever but relies entirely upon abstract conceptions of a clinical entity. Although there is no question that in the early part of the 19th century the therapeutic use of ar-

senic was much abused, a reaction had already set in as evidenced by the warning of its dangers which Charles Darwin received in his early twenties from his physician father. Although the author mentions the Manchester beer epidemic he fails to recognize the nature of the unique feature which suggested arsenic. Those of us trained in medicine fifty years ago and surrounded by arsenic were fully aware of its long-range effects despite the statement (page 75) that the present aversion to arsenic "arose not so long ago." Our teachers, trained in the latter half of the previous century, provided the admonitions as did the reviewer's father, an intimate of Thomas Henry Huxley, who possessed a considerable reputation for recognition of poisoning in the use of insecticides and other covert sources of arsenic.

It is a pity that the author did not take more seriously the warning which he quotes (page 8) to the effect that in cases in which it is difficult to establish a diagnosis "once it is cooked up it can be elaborated *ad lib,*" otherwise he would have avoided the blunder of assuming from Darwin's purchase of "Lavender water" that he was concocting his own Fowler's solution. Even as a medical student Darwin would know something of the distinction between the water and the compound tincture or the oil of lavender.

But then "paper" autopsies always have their reservations and no harm done.

J. B. deC. M. Saunders, M.D.

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INTELLIGENCE—Genetic and Environmental Influences—Edited by Robert Cancro, M.D., Professor, Department of Psychiatry, University of Connecticut, School of Medicine. Grune & Stratton, Inc., 111 Fifth Avenue, New York, NY (10003), 1971. 312 pages, $12.50.

Dr. Cancro, editor of recent volumes on schizophrenia research and theory, has once again stimulated productive scholarship in an area of social importance. His current effort is a data-based, theoretical approach to the study of individual intellectual abilities. The topic is a controversial one to say the least. Rarely do academic concerns attain the degree of heated public debate now focused on the concept of "intelligence." Furor over the issue of possible *racial* differences in level of intelligence has embroiled scholars, educators, politicians and community leaders in a continuing rancorous interchange. This context was an experiential reality for the contributors to this volume as they participated in a conference on intelligence at the University of Illinois. Like others of its kind, the conference was a focus of bomb warnings, threats, apprehensions and fears.

The resulting book addresses itself to three basic areas: (a) definitions and refinements of the concept of intelligence (written by such notables as Cattell, Humphreys, Wechsler and Merrifield); (b) a well-rounded survey of the genetic issues (including papers by Jensen, Hirsch, Eckland, Li and Vandenberg—among others); and (c) a less comprehensive series of papers having an environmental orientation (prepared by Bijou, Gordon, Greenfield, Hunt and Kirk). The material is uniformly well-written. Because of its clarity and format, the volume is admirably suited for use in the medical or graduate school curriculum. It is valuable to the clinician and scholar in that it provides a brief compendium of the issues written by acknowledged experts.

Complex issues related to intelligence (race, non-intellective factors influencing intelligence, polygenetic foundations of intellectual potential) are treated with new data and reasoned perspective. Of special importance are papers by Vandenberg (a lucid account of newest trends in genetic research); Hirsch (biosocial consequences of behavior-genetic analysis); and McV. Hunt and Kirk (social aspects of intelligence). It is regrettable that John R. Horn, present at the conference but unable to contribute to the volume, did not provide an analysis of the difficult measurement and statistical problems involved in the development of a socially useful concept of intellective competence. Also, it is not clear why the editor failed to provide a needed final integrative chapter. Perhaps the field, with all its complexity and discord, simply is not amenable to more than the most tentative synthesis. Nevertheless, a summary of the basic achievements of the conference, independent of the papers, would have been useful. Despite these limitations, this volume clearly provides constructive directions for further thought and research.

Ultimately, the timeliness of this book may be its greatest contribution. Recently a court decision banned the use of so-called "IQ tests" in San Francisco because of alleged discrimination against Black and other ethnic minority students in the public school system. Spokesmen for this point of view have forcefully argued that "standardized" tests of intellectual ability lead to a tracking system which inevitably involves a self-fulfilling prophecy of restricted opportunity and achievement among individuals designated as possessing poorer ability at the time of initial assessment. Without doubt, much of the classical work of Binet, Terman, Merrill and Wechsler has been thoughtlessly incorporated by the educational establishment of the American culture. It is hoped that recent developments within the academic world, as signaled by the Illinois conference, may provide the basis for more sensitive understanding of human abilities as well as stimulate more productive, responsive educational environments.

C. Clifford Attkisson, Ph.D.

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REHABILITATION MEDICINE—Third Edition—Howard A. Rusk, M.D., Professor and Chairman of the Department of Rehabilitation Medicine, New York University Medical Center, New York City. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1971. 687 pages, $21.00.

This third edition of a classic work is no longer subtitled "A Textbook in Physical Medicine and Rehabilitation." Its present title is more accurate. It comprehensively covers the field, dividing the task into 2 sections.

The first section covers the principles of therapy, prescriptions, devices, etc. The chapter on orthotics and prosthetics is greatly expanded and improved. It serves as an excellent introduction to principles for the use of upper and lower extremity devices. One would like to see references to thermoplastic materials in orthotics included. Principles of Housing is noteworthy in the presentation of the problem of architectural barriers for the disabled, and the simple procedures necessary to enable the patient to function with a minimum of assistance in his home.

The second section covers specific areas of rehabilitation. The new chapter on Pulmonary Problems is exceptional in its coverage of pulmonary function testing, management of the COPD patient and respiratory insufficiency in neuromuscular and skeletal disorders. Too often the significance of alveolar hypoventilation in the care of the paraplegic or scoliotic is not appreciated in other tomes. Cardiovascular Diseases is presented in much greater depth than in previous editions, and includes stress testing, and exercise prescriptions. In the section on amputee management, I would take exception to the concept that training starts after surgery. Indeed, it starts before.

This text is a must in its field. It contains information that is easy to gather from its pages, for every practitioner, from pediatrics to geriatrics, medicine and surgery. The physician will have repeated need for this volume for effective care of temporary as well as permanent disability.

Sheldon Berrol, M.D.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Beaton, Alexander Haitt, San Rafael. Died November 20, 1972, aged 48. Graduate of Yale University School of Medicine, New Haven, 1947. Licensed in California in 1954. Doctor Beaton was a member of the Marin Medical Society.

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Bloedau, Emanuel L., Santa Rosa. Died October 29, 1972 in Santa Rosa, aged 62. Graduate of the University of Louisville School of Medicine, 1937. Licensed in California in 1941. Doctor Bloedau was a member of the Sonoma County Medical Association.

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Carpenter, Harold Clinton, Berkeley. Died November 5, 1972 in Berkeley of pulmonary embolism, aged 69. Graduate of the University of Rochester School of Medicine and Dentistry, New York, 1930. Licensed in California in 1931. Doctor Carpenter was a member of the Alameda-Contra Costa Medical Association.

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Cobb, Dudley Manchester, Jr., Los Angeles. Died October 28, 1972 in London, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1937. Licensed in California in 1937. Doctor Cobb was a member of the Los Angeles County Medical Association.

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Crail, Howard W., Clearlake Oaks. Died September 25, 1972 in Clearlake Oaks, aged 54. Graduate of Northwestern University Medical School, Chicago, 1942. Licensed in California in 1943. Doctor Crail was a member of the Mendocino-Lake County Medical Society.

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Eldridge, Ernest B., Tarzana. Died March 27, 1972 in Los Angeles of cancer, aged 77. Graduate of State University of New York Upstate Medical Center, Syracuse, 1925. Licensed in California in 1948. Doctor Eldridge was a member of the Los Angeles County Medical Association.

Eldridge, Samuel, Crockett. Died November 10, 1972 of injuries received in an automobile accident, aged 68. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Doctor Eldridge was a member of the Alameda-Contra Costa Medical Association.

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Hull, Roswell L., Hollister. Died November 9, 1972 in Hollister, aged 74. Graduate of Tulane University School of Medicine, New Orleans, 1929. Licensed in California in 1929. Doctor Hull was a retired member of the San Benito County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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Jacobs, Joseph, Los Angeles. Died October 1, 1972, aged 94. Graduate of the University of Wooster Medical Department, Cleveland, 1907. Licensed in California in 1911. Doctor Jacobs was a member of the Los Angeles County Medical Association.

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Katz, Leonard, Fresno. Died October 27, 1972 in Fresno, aged 65. Graduate of University of Maryland School of Medicine, Baltimore, 1932. Licensed in California in 1941. Doctor Katz was a retired member of the Fresno County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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McCrea, John Henry, Redondo Beach. Died November 7, 1972 in Redondo Beach of heart disease, aged 62. Graduate of the University of Vermont College of Medicine, Burlington, 1938. Licensed in California in 1956. Dr. McCrea was a member of the Los Angeles County Medical Association.

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Mitchell, William John, San Gabriel. Died October 29, 1972 in Pasadena of carcinoma of the bladder, aged 65. Graduate of University of Southern California School of Medicine, Los Angeles, 1935. Licensed in California in 1935. Doctor Mitchell was a member of the Los Angeles County Medical Association.

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Newman, Harry W., Seal Beach. Died September 17, 1972 in Long Beach of coronary artery disease, aged 73. Graduate of Rush Medical College, Chicago, 1930. Licensed in California in 1930. Doctor Newman was a member of the Los Angeles County Medical Association.

PAULL, ROSS C., La Jolla. Died November 5, 1972 in La Jolla, aged 70. Graduate of Harvard Medical School, Boston. 1927. Licensed in California in 1928. Doctor Paull was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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PEARSON, ALVIRDO WALLACE, Encino. Drowned in a boating accident, April 22, 1972, aged 62. Graduate of Rush Medical College, Chicago, 1936. Licensed in California in 1936. Doctor Pearson was a member of the Los Angeles County Medical Association.

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REUBEN, PHILIP ROBERT, Beverly Hills. Died October 29, 1972 in Beverly Hills of metastases carcinoma, aged 63. Graduate of State University of Iowa College of Medicine, Iowa City, 1935. Licensed in California in 1936. Doctor Reuben was a member of the Los Angeles County Medical Association.

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ROSE, HARRY L., Shell Beach. Died October 1, 1972 in Shell Beach of bacterial endocarditis, aged 78. Graduate of the University of Illinois College of Medicine, Chicago, 1919. Licensed in California in 1952. Doctor Rose was a member of the San Luis Obispo County Medical Society.

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SPENCER, GORDON A., Morgan Hill. Died November 9, 1972 in Gilroy, aged 64. Graduate of Cornell University Medical College, New York, 1936. Licensed in California in 1945. Doctor Spencer was a member of the Santa Clara County Medical Society.

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STONE, EVERETT M., Riverside. Died November 3, 1972 in Riverside, aged 72. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1931. Licensed in California in 1932. Doctor Stone was a member of the Riverside County Medical Association.

TONGE, EDWARD BURNETT, Modesto. Died October 27, 1972 in Modesto, aged 44. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1955. Licensed in California in 1956. Doctor Tonge was a member of the Stanislaus County Medical Society.

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VAUGHN, JOHN ORREN, Santa Monica. Died November 25, 1972 in Santa Monica of heart disease, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1929. Doctor Vaughn was a member of the Los Angeles County Medical Association.

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WALSH, JOHN GREGORY, Sacramento. Died November 19, 1972 in Sacramento, aged 59. Graduate of Marquette University School of Medicine, Milwaukee, 1938. Licensed in California in 1938. Doctor Walsh was a member of the Sacramento County Medical Association.

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WATSON, ALLAN RAYMOND, Eureka. Died November 23, 1972 in Eureka of heart disease, aged 77. Graduate of University of California Medical School, San Francisco-Berkeley, 1924. Licensed in California in 1924. Doctor Watson was a retired member of the Humboldt-Del Norte County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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WILLIAMS, JOSEPH B., Los Angeles. Died November 4, 1972 in Los Angeles of cardiac insufficiency, aged 69. Graduate of Washington University School of Medicine, St. Louis, 1927. Licensed in California in 1930. Doctor Williams was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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YOST, CHARLES WILLIAM, Arcata. Died November 18, 1972 in Eureka of cerebral hemorrhage, aged 62. Graduate of the University of Cincinnati College of Medicine, 1938. Licensed in California in 1964. Doctor Yost was an associate member of the Humboldt-Del Norte County Medical Society.

102nd Annual Session

California Medical Association

March 10 to 14, 1973

Disneyland Hotel

Anaheim

102nd Annual Session Program

and Second Western States Invitational Scientific Assembly

Disneyland Hotel
Anaheim

March 10-14, 1973

- *Scientific Section Programs*
- *Special Conferences*
- *Scientific and Technical Exhibits*
- *Meetings of the House of Delegates*

California Medical Association

CALIFORNIA MEDICAL ASSOCIATION 102nd ANNUAL SESSION

March 10-14, 1973—Disneyland Hotel Convention Complex, Anaheim

DAILY SCHEDULE

SATURDAY, MARCH 10	Room	Morning	Afternoon	All Day
Section Meetings:				
Allergy	Magnolia D			8:50
General and Family Practice	Embassy West I			8:00
Ophthalmology	2525 Dupont Drive, Irvine*		1:00	
Pathology	Embassy West III	9:00		
Physical Medicine and Rehabilitation	Pacific		2:00	
Special Conferences:				
Occupational Health Conference	Embassy West II	9:00		
American College of Chest Physicians	Magnolia B			8:30
Second Congress on Health of the School Age Child	Anaheim Convention Center—Santa Ana 1 and 2			9:00
Seventh Annual Cancer Symposium	Embassy East IV, V and VI		2:00	
CMA House of Delegates—Opening Session	Center Ballroom		1:00	
Scientific and Organizational Exhibits	Exhibit Hall			9:00

*Transportation will be available from the Disneyland Hotel at 12:30 p.m.

SUNDAY, MARCH 11				
Section Meetings:				
Anesthesiology/Otolaryngology	Embassy West III	9:00		
Anesthesiology	Embassy West III		1:30	
Chest/Internal Medicine	Magnolia B	9:00		
Chest/Industrial Medicine†	Magnolia B		2:00	
Dermatology	Embassy East IV	8:30		
Ophthalmology	Embassy East V			9:00
Otolaryngology/Neurology	Magnolia A		1:30	
Plastic Surgery/General and Family Practice	Magnolia D			9:00
Psychiatry	Embassy East VI			9:00
Special Conferences:				
California Tumor Registry Pathology Conference	Embassy West I and II			9:00
Second Congress on Health of the School Age Child	Anaheim Convention Center—Santa Ana 1 and 2	9:00		
Treatment for Alcoholism and Other Drug Abuse	Magnolia C			9:00
Scientific and Organizational Exhibits	Exhibit Hall			9:00

†The Industrial Medicine and Surgery Section Meeting will be held at 1:30 p.m. in Magnolia Room B.

MONDAY, MARCH 12	Room	Morning	Afternoon	All Day
Section Meetings:				
General Surgery	Magnolia B		1:20	
Obstetrics and Gynecology/Urology	Magnolia C	9:00		
Obstetrics and Gynecology	Magnolia C		2:15	
Preventive Medicine and Public Health	Magnolia D			8:30
Urology	Magnolia A		1:30	
Special Conferences:				
Cardiac Emergencies	Anaheim Convention Center			9:00
Disaster and Emergency Medical Services	Embassy West III			9:00
Medical Data Processing Conference	Embassy West I		1:00	
Medicine and Religion	Embassy West I	9:30		
Scientific and Organizational Exhibits	Exhibit Hall			9:00
TUESDAY, MARCH 13				
Section Meetings:				
Orthopedics/Pediatrics/Radiology	Embassy West I and II		2:00	
Pediatrics	Embassy West I	9:00		
Special Conference:				
Cardiac Emergencies	Anaheim Convention Center	9:00		
CMA HOUSE OF DELEGATES	Center Ballroom		1:30	
Scientific and Organizational Exhibits	Exhibit Hall			9:00
WEDNESDAY, MARCH 14				
CMA HOUSE OF DELEGATES	Center Ballroom	9:00 to conclusion of business		

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ACKNOWLEDGEMENT

The 1973 Annual Scientific Assembly brings to a close my term as chairman of the CMA Committee on Scientific Assemblies.

My thanks go to a loyal and hard-working committee as well as to the more than 300 members of the 21 advisory panels to the scientific sections, who constitute the planning committees for the Assembly. Thanks are also due to the exceptionally competent and professional CMA staff. Together we have seen the Annual Session grow in stature to become an educational meeting of outstanding quality, quite different in character and scope from the "traditional" medical meeting. My parting wish is that, as the Assembly continues to develop, my successor as chairman may have as much satisfaction as I have felt in the last six years, and that the educational quality of the meeting continually improves as a part of the innovative and profoundly influential program of the California Medical Association in continuing medical education.

JOHN B. DILLON, M.D., *Chairman*
Committee on Scientific Assemblies

California Medical Association



JEAN F. CRUM, M.D., *President*



THOMAS ELMENDORF, M.D., *President-Elect*

Information

NOTE WELL:

Unless otherwise indicated, meetings will all take place at the Disneyland Hotel Convention Complex. Some meetings have been scheduled at the Anaheim Convention Center, a quarter mile away.

BADGES:

It is important that badges be worn at all times. Admission to scientific meetings is by badge only.

COUNCIL:

The Council will meet on Friday at 3:00 p.m. in the South Lounge. Executive sessions will be posted on the hotel schedule boards.

HOUSE OF DELEGATES:

For meeting times, places and agenda—see pages 2, 36. The list of Delegates and Alternates appears on pages 33, 34, 35.

EMERGENCY CALLS AND MESSAGES:

Convention Emergency Call Number—(714) 535-8171, Extension 1487, from 9:00 a.m. to 5:00 p.m., Saturday, March 10 through Wednesday, March 14.

MESSAGE CENTER:

Provided through the courtesy of the Pacific Telephone Company.

Marina Tower Lobby, Disneyland Hotel—(714) 535-8171, Extension 1487; South Lounge Area, Anaheim Convention Center—(714) 635-8550. *Hours:* 9:00 a.m. to 5:00 p.m.

The Association will *attempt* to transmit *emergency* messages to individual physicians. Each physician should notify his own office of the exact times and locations of meetings he plans to attend.

Routine Messages: Will be kept at the Message Center in the Marina Tower Lobby, Disneyland Hotel.

Physicians are requested to check with the Message Center at least once daily.

INDEX TO PARTICIPANTS:

See pages 8, 9, 10.

TECHNICAL EXHIBITS:

Exhibit Hall, Disneyland Convention Complex.

INFORMATION DESK:

The information desk will be located in the Marina Tower Lobby, Disneyland Hotel, and will be open daily from 9:00 a.m. to 5:00 p.m., Saturday, March 10 through Wednesday, March 14.

REGISTRATION:

Registration will take place in the Center Lounge, Disneyland Hotel, starting Friday, March 9 at 4:00 p.m. Saturday registration will begin at 8:00 a.m.

All members, guests and visitors are requested to register immediately on arrival. *There will be a $10.00 registration fee for attendees who are not CMA members.* The following individuals will be *exempt* from the registration fee: physicians who are CMA members, their wives and families; medical students and interns; other health professionals (e.g., nursing students); program participants and medical executives (county and specialty societies in and out of California).

Admission to the conferences and section meetings as well as to the exhibit area is by badge only.

Members wishing to vote in specialty sections must indicate the appropriate section when registering; voting in other sections will not be allowed.

QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION:

All M.D.s with credentials showing that they hold a valid license to practice medicine (e.g., membership card in CMA, AMA or county medical society).

Medical students upon presentation of credentials from their medical school (e.g., membership card in student medical association or letter from dean's office).

Medical assistants upon presentation of letter from a physician-employer or A.A.M.A. membership card.

Military paramedical personnel upon presentation of a letter from their commanding officer.

Dentists (D.D.S.); *Doctors of Veterinary Medicine* (D.V.M.); *registered nurses* (R.N.); *student nurses; x-ray technicians; allied public health personnel and others* will be admitted provided they have proper identification.

ALL QUESTIONS ON ADMISSION will be passed upon by a member of the Committee on Registration present at the desk.

Out-of-State Guests

SECTIONS and SPECIAL CONFERENCES

- *Allergy*

 John E. Salvaggio, M.D., Department of Internal Medicine, Tulane University School of Medicine, New Orleans

- *Anesthesiology, Otolaryngology*

 John Tucker, M.D., Professor of Otolaryngology and Bronchoesophagology, Hahneman Medical College, Philadelphia

- *Chest Diseases, Internal Medicine*

 Juro Wada, M.D., Professor of Surgery, University of Medicine, Sapporo, Japan; Visiting Professor, Thoracic Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee

 Albert Starr, M.D., University of Oregon Medical School, Portland

- *Chest Diseases, Industrial Medicine*

 LeRoy Lapp, M.D., Chief, Medical Research Branch, Appalachian Laboratory for Occupational Respiratory Diseases, Department of HEW, US Public Health Service, Morgantown, West Virginia

 I. J. Selikoff, M.D., Mount Sinai School of Medicine of The City University of New York, New York City

 George H. R. Taylor, AFL-CIO Standing Committee on Safety and Occupational Health, Washington, D.C.

- *General and Family Practice*

 Robert Brittain, M.D., Inter-Hospital Education Association, Englewood, Colorado

 Harold Cross, M.D., Promis Clinic, Hampden Highlands, Maine

- *General and Family Practice, Plastic Surgery*

 Paul Daines, M.D., Coordinator, NRMP Intermountain District for Continuing Medical Education, Montpelier, Idaho

- *General Surgery*

 Edward R. Woodward, M.D., Professor and Chairman, Department of Surgery, University of Florida College of Medicine, J. Hillis Miller Health Center, Gainesville

- *Obstetrics and Gynecology*

 Paul C. MacDonald, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical School at Dallas

- *Ophthalmology*

 Eugene R. Folk, M.D., Associate Professor of Ophthalmology, Abraham Lincoln School of Medicine, University of Illinois, Chicago; Attending Ophthalmologist on the Motility Service, Illinois Eye and Ear Infirmary, Skokie

- *Orthopedics, Pediatrics, Radiology*

 Walter P. Blount, M.D., Emeritus Clinical Professor of Orthopedics, Medical College of Wisconsin, Milwaukee

 Frederick N. Silverman, M.D., Professor of Radiology, University of Cincinnati College of Medicine

- *Pediatrics*

 Alan K. Done, M.D., Bureau of Drugs, Food and Drug Administration, Washington, D.C.

- *Physical Medicine and Rehabilitation*

 Jerome Gersten, M.D., Professor and Chairman, Department of Physical Medicine and Rehabilitation, University of Colorado Medical Center, Denver

- *Cancer Symposium*

 Alando J. Ballantyne, M.D., Associate Professor of Surgery, University of Texas Medical School at Houston; Surgeon, Head and Neck, Department of Surgery, M. D. Anderson Hospital and Tumor Institute, Houston

 Harry S. Goldsmith, M.D., Samuel D. Gross Professor of Surgery; Chairman, Department of Surgery, Jefferson Medical College, Philadelphia.

 Alfred S. Ketcham, M.D., Clinical Director and Chief of Surgery Branch, National Cancer Institute, Bethesda, Maryland

- *Alcoholism/Dangerous Drugs Conference*

 Karl J. Deissler, M.D., Luzern, Switzerland

 Roger O. Egeberg, M.D., Special Assistant to the President on Health Affairs; Secretary of HEW on Health Matters, Department of Health, Education and Welfare, Office of the Secretary, Washington, D.C.

 R. Edward Quass, M.D., Tucson, Arizona

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make reservations now and plan to attend . . .

CMA PRESIDENTS' DINNER

Sunday evening, March 11

Disneyland Hotel, Anaheim

Dinner will be at 7:30 p.m., immediately following the traditional Presidents' Reception at the CMA Annual Session, and the leaders of the CMA and the Woman's Auxiliary to the CMA will be honored. The dinner will feature live music, entertainment, and awards and presentations formerly made during the House of Delegates sessions.

Tickets are $10.50 each. Tables seat 10 persons. For reservations, send check made out to WA-CMA to: Woman's Auxiliary to CMA, 10161 Broadview Place, Santa Ana 92705.

California Medical Association

CERTIFICATE

IN

CONTINUING MEDICAL EDUCATION

SPECIAL ANNOUNCEMENT

Each scientific program acceptable for Category 1 credit is so designated:

Acceptable for Category 1 Credit under
the CMA Certification Program

The majority of the other educational and scientific programs are acceptable for informal credit.

PHYSICIANS SHOULD REPORT
THE ACTUAL NUMBER OF
PROGRAM HOURS ATTENDED

Special Conferences

SATURDAY, MARCH 10 Embassy Rooms East IV, V & VI

AMERICAN CANCER SOCIETY CALIFORNIA DIVISION

SEVENTH ANNUAL CANCER SYMPOSIUM

The Black Cancer—A Symposium on Melanoma

Chairman of Planning Committee and Program Moderator: James T. Helsper, M.D., Pasadena

2:00—**Welcome**—James T. Helsper, M.D.

2:05—**Is It Melanoma?**—James T. Helsper, M.D.

2:10—**Depth of Invasion: Is This a Basis for Prognosticating in Melanoma?**—John H. Mehnert, M.D., San Diego

2:30—**The Joint Committee on Melanoma Staging—What Are Conclusions Thus Far?**—Alfred S. Ketcham, M.D., Bethesda, Maryland

2:50—**Discussion**—Questions and Answers

3:00—**How Are We Doing in Cutaneous Melanomas of the Head and Neck?**—Alando J. Ballantyne, M.D., Houston

3:20—**Is Prophylactic Node Dissection Worthwhile in Melanoma? How About Trunk and Limb?**—Harry S. Goldsmith, M.D., Philadelphia

3:40—**Discussion**—Questions and Answers

3:50—**What is the Place of Immunotherapy in the Management of Melanoma?**—Donald L. Morton, M.D., Los Angeles

4:10—**How Effective Is Chemotherapy in Melanoma?**—Joseph R. Bateman, M.D., Los Angeles

4:30—**Is Radiation Therapy Worthwhile in Melanoma?**—Frederick W. George, III, M.D., Los Angeles

4:50—**Discussion**—Questions and Answers

5:00—"**Melanomas**"—A New Film Produced by the American Cancer Society (25 minutes)

Acceptable for Category 1 Credit under the CMA Certification Program

CARDIAC EMERGENCIES

A Postgraduate Workshop Cosponsored by the

American College of Cardiology and California Medical Association

Course Directors: Arthur Selzer, M.D., San Francisco; H. J. C. Swan, M.D., Los Angeles; Keith E. Cohn, M.D., San Francisco

Educational Consultant: Rodger Shepherd, M.D., San Francisco

Method of Instruction

Three half-day sessions will deal with three separate subjects. Each session will consist of an hour and a half workshop conducted in groups of 15, where the issues will be presented in depth under a discussion leader. The final hour will consist of a plenary session chaired by one of the course directors who will identify the most important points as indicated by reports from the discussion leaders. Each advance registrant will receive a syllabus in advance of the course which will contain:

1. The case histories of patients who will be discussed during the workshop sessions,
2. Questions related to the important issues in each case and
3. Selected bibliographical list

MONDAY, MARCH 12 Anaheim Convention Center

This postgraduate workshop is designed for the practicing physician. A series of cases will be presented which will exemplify various emergencies arising in patients with heart disease. During the sessions the critical issues in the diagnosis and treatment of such emergencies will be identified and discussed.

First Session—9:00 a.m. to Noon

Arrhythmias

Critical Issues: Tachyarrhythmias, ventricular fibrillation, Stokes-Adams syncope, warning of impending arrhythmias

9:00—**Workshops**

10:30—**Intermission**

11:00—**Plenary Session**—Arthur Selzer, M.D., San Francisco

Second Session—2:00 p.m. to 5:00 p.m.

Shock-Like States

Critical Issues: Pre-infarction states, early stages of acute myocardial infarction, cardiogenic shock

2:00—Workshops

3:30—Intermission

4:00—Plenary Session—H. J. C. Swan, M.D., Los Angeles

TUESDAY, MARCH 13 Anaheim Convention Center

Third Session—9 a.m. to Noon

Cardiorespiratory Failure

Critical Issues: Acute pulmonary edema, "low output failure," respiratory failure, failure in severe aortic stenosis

9:00—Workshops

10:30—Intermission

11:00—Plenary Session—Keith Cohn, M.D., San Francisco

Acceptable for Category 1 Credit under the CMA Certification Program

Minimum registration, 50; maximum, 150. Advance registration is requested. Registration fee $50, which includes workshops, plenary sessions and syllabus.

Faculty of Workshops: Members of Cardiology Departments of Presbyterian Hospital of Pacific Medical Center, San Francisco, and Cedars-Sinai Medical Center, Los Angeles.

For information about registration contact:
Miss Mary Anne McInerny
American College of Cardiology
9650 Rockville Pike
Bethesda, Maryland 20014

SUNDAY, MARCH 11 Embassy Rooms West I & II

California Tumor Tissue Registry PATHOLOGY CONFERENCE

Sponsors: American Cancer Society, California Division; University of Southern California School of Medicine

Pigmented and Other Tumors of the Skin

9:00 to 12:00

Chairman: Seth Haber, M.D., Santa Clara

Moderators: Donald Alcott, M.D., Los Gatos; Richard W. Sagebiel, M.D., San Francisco

2:00 to 5:00

Continuation of morning session

Registration Fee:

Pathologists and other physicians: $50.00 (This includes attendance, slides, protocol, and addenda.) $25.00—Attendance only

Residents and Interns: $35.00 (This includes slides, protocol and addenda.) No charge for attendance only.

Those wishing to attend are requested to register with Weldon K. Bullock, M.D., Executive Director, California Tumor Tissue Registry, Los Angeles County-University of Southern California Medical Center, 1200 North State Street, Los Angeles 90033.

Acceptable for Category 1 Credit under the CMA Certification Program

MONDAY, MARCH 12 Embassy Room West III

DISASTER AND EMERGENCY MEDICAL SERVICES

Morning Session

Jointly sponsored by
CMA Commission on Community Health Services
CMA Committee on Disaster Medical Care
CMA Committee on Emergency Medical Care
American College of Emergency Physicians

Moderator: Arnold Niemeyer, M.D., San Diego

9:00—**Panel on Lessons Learned from the 1971 Los Angeles Earthquake**
Members of the Panel: Edward Russell, Los Angeles; Stephen Gamble, Los Angeles; Emile L. Meine, Jr., M.D., Panorama City; Max H. Weil, M.D. Los Angeles

10:30—**Panel on Education for Disaster and Emergency Medical Services**

Members of the Panel: Gaylord Ailshie, Torrance; Gail V. Anderson, M.D., Los Angeles; Daniel Bessesen, M.D., San Diego; James Brill, M.D., Los Angeles; John T. Celentano, M.D., Los Angeles; Leon S. Richman, M.D., Los Angeles

1. **Doctors and Paramedics in Triage**—Gaylord Ailshie, Torrance
2. **Training of New Emergency Health Professionals**—Gail V. Anderson, M.D., Los Angeles
3. **In-Hospital Disaster Planning**—Daniel Bessesen, M.D., San Diego

11:40—**Discussion and Questions from the Audience**

Afternoon Session

Sponsored by
CMA Committee on Disaster Medical Care

Symposium on Aviation Safety

Chairman: Marvin B. Hays, M.D., Eureka

1:45—**Opening Remarks**—Wayne P. Chesbro, M.D., Berkeley

1:50—**Orientation**—Marvin B. Hays, M.D., Eureka

1:55—Welcome—Jean F. Crum, M.D., Downey

2:00—**Congressional Legislation Relative to Aviation Safety**—Honorable Jerry Pettis, Congressman, California's 33rd District, Washington, D.C.

2:30—

PANEL PRESENTATION

The Physician-Pilot Answer to Hijacking

Moderator: Charles I. Barron, M.D., Burbank

Participants: Oscar Cleal, former air carrier pilot, Hughes Aircraft Corporation, Menlo Park; Chris Boyce, airline stewardess, Palo Alto; Carl B. Younger, M.D., psychiatrist and flying physician, Burbank; Chet Casselman, News Director, KSFO Radio, San Francisco

3:20—**Questions and Answers**

3:40—**Aviation Safety Record Review of 1972**

4:00—**Summary**

SATURDAY, MARCH 10 — Embassy Room West II

Early Intervention in the Emotional Problems of Individuals in Their Work Environment

Presented by
CMA Committee on Occupational Health

Chairman: Robert S. Hockwald, M.D., San Francisco

Moderator: Allen Enelow, M.D., San Francisco

9:00—The program will consist of a series of videotaped interviews followed by discussion from a panel, including an industrial psychiatrist, industrial psychologist, industrial medical director and a physician involved with industrial consultation. This program will be of interest to physicians.

MONDAY, MARCH 12 — Embassy Room West I

Is Marriage Passé?

Presented by
CMA Committee on Medicine and Religion

Moderator: Albert E. Long, M.D., San Francisco

9:30—Proponents of alternatives to marriage will give their opinions on the merits of communal living, trial marriage, the single parent, the extended family, and the modern family. A panel of a physician, a clergyman, and a counselor will discuss the medical, moral and social aspects of marriage and its alternatives.

Panelists: Roy R. Shoaf, M.D., Los Angeles; Floyd M. Anderson, Ed.D., Los Angeles; Gary Collins, B.D., M.A., Riverside

SATURDAY, MARCH 10 — Magnolia Room B

POSTGRADUATE COURSE ON CARDIOPULMONARY MEDICINE AND SURGERY

Program Chairman: Alfred Goldman, M.D., Palm Springs

Presented by the CMA Section on Chest Diseases

Cosponsored by the California Chapter, American College of Chest Physicians and the California Thoracic Society

Registration Fee: $25 (includes luncheon)

Make checks payable to: California Chapter, American College of Chest Physicians

Mail registration fee to:
California Chapter, American College of Chest Physicians
424 Pendleton Way
Oakland, Ca 94621

Registration closes March 5, 1973

(Please use Reservation Form printed on page 28.)

Pulmonary Session

Chairman: Jerome H. Kay, M.D., Los Angeles

8:30—Registration

8:45—**Pulmonary Function in Thoracic Disease**—Philip Gold, M. D., Los Angeles

9:00—**The Neuropathology of Thoracic Tumors**—Jeff Minckler, M. D., Palm Desert

9:15—**Current Approaches for Thoracic Tumors**—Lyman A. Brewer, III, M. D., Los Angeles

9:40—**Recent Advances in Radiation Therapy for Tumors of the Lung**—Henry L. Jaffe, M.D., Los Angeles

10:00—**Break**

10:10—**Sternal Turnover in Surgery for Funnel Chest**—Juro Wada, M.D., Sapporo, Japan

10:30—**Respiratory Distress Syndrome: Etiology and Diagnosis**—Steven Levy, M. D., Los Angeles

10:50—**Treatment of Respiratory Distress Syndrome**—Daniel H. Simmons, M.D., Los Angeles

11:10—**The Clinical Diagnosis of Incomplete and Complete Pulmonary Infarction**—Oscar J. Balchum, M.D., Ph.D. Los Angeles

11:30—**The Management of Incomplete and Complete Pulmonary Infarction**—Edward Seinfeld, M.D., Claremont

11:50—**Needle Lung Biopsy, Bronchial Brushing and Mediastinoscopy in Management of Chest Diseases**—Frederick Firestone, M.D., Irvine

12:15—**Luncheon**
Presiding: Alfred Goldman, M.D., Palm Springs

12:30—**Luncheon Address: Conservation of Lung Function in Thoracic Surgery**—Lyman A. Brewer, III, M.D., Los Angeles

Coronary Session

Chairman: Bertram Meyer, M.D., Los Angeles

2:00—Medical Management of Coronary Artery Disease—Eliot Corday, M.D., Beverly Hills

2:35—Acute Coronary Insufficiency Syndromes—Jack Matloff, M.D., Los Angeles

3:00—Surgical Treatment of Coronary Artery Disease—Jerome H. Kay, M.D., Los Angeles

3:25—Break

3:40—Lessons Learned During Four Years' Experience with Direct Coronary Artery Revascularization Procedure—John E. Connolly, M.D., Anaheim

Acceptable for Category 1 Credit under the CMA Certification Program

SECOND CONGRESS ON HEALTH OF THE SCHOOL AGE CHILD

Dedicated to Dorothy Nyswander, Health Educator

SATURDAY & SUNDAY, MARCH 10 & 11 — Anaheim Convention Center, Santa Ana Rooms 1 and 2

Chairman: Tom W. Robinson, M.D., Newport Beach

Chief Sponsor: California Medical Association Committee on School and College Health

Additional Sponsors: American School Health Association; California Association for Health, Physical Education and Recreation; California Association for Neurologically Handicapped Children; California Congress of Parents and Teachers; California Home Economics Association; California Interagency Council on Family Planning; California Medical Association V.D. Task Force; California Nurses' Association; California Regional Medical Programs—Areas IV, V and VIII; California School Boards Association; California School Health Association; California School Nurses Organization; California State Department of Education; California Teachers Association; California Youth Authority; Comprehensive Health Planning—Bay Area, Channel Counties, Los Angeles County and Superior California; Los Angeles County Department of Mental Health; National Council of Negro Women; Orange County Medical Center; Planned Parenthood/World Population California Affiliates; St. Mary's Hospital and Medical Center—San Francisco; Society for Public Health Education—Northern California Chapter; University of California, Irvine, California College of Medicine—Department of Pediatrics; University of California, San Diego, School of Medicine, Department of Pediatrics.

Reservation fee: $20, includes luncheons Saturday and Sunday, March 10 and 11.

(Please use Reservation Form printed on page 28.)

SATURDAY, MARCH 10 — Santa Ana Rooms 1 and 2

Conference Chairman: B. Otis Cobb, M.D., Woodland

Keynote Symposium: The Spectrum of Health of Young People

9:00—Introductory Remarks

9:05—Keynote Address—Frederick B. Hodges, M.D., Berkeley

9:45—Questions and Answers Session

10:00—Second Keynote Address—Patricia Hill, M.P.H., Sacramento

10:45—Questions and Answers Session

11:00—Recess

11:15—Third Keynote Address and Summation—B. Otis Cobb, M.D., Woodland

11:45—Questions and Answers Session

12:00—Luncheon — Anaheim Room

Guest Speaker: The Honorable George R. Moscone, State Senator, Sacramento

A Child Health Policy for California

2:00—Position Paper Reactor Panel I — Santa Ana Room 1

Relationships of Youth with Society and Educational Institutions

Moderator: Ruth Glick, Ph.D., San Francisco

Position Paper: Victor Eisner, M.D., Berkeley

Panel Members: Irving Berkovitz, M.D., Beverly Hills; Helen Davis, Los Angeles; Wilson Grace, San Bernardino; Duane Hall, Newbury Park; Stuart Kaufer, Berkeley; Maxine B. Wainman, R.N., Los Angeles; Kenneth R. Walker, Los Angeles

3:00—Questions and Answers Session

3:30—Position Paper Reactor Panel II — Santa Ana Room 1

Interpersonal Relationships and Responsible Parenthood

Moderators: Cheryl Kleinhammer, Berkeley, and James C. Voss, Jr., Santa Rosa

Position Paper: Roger Betsworth, D.D., Huntington Beach

Panel Members: Allure Jefcoat, Walnut Creek; Jane Leggett, Rancho Cordova; Maxine Sehring, M.D., Walnut Creek

4:30—Questions and Answers Session

(Continued on next page)

2:00—Position Paper Reactor Panel III — Santa Ana Room 2

School Health Personnel — Old and New Roles

Moderator: Margaret Williamson, Santa Ana

Position Paper: George Cunningham, M.D., Berkeley

Panel Members: Mary K. McOwen, Riverside; Thomas Nelson, M.D., Irvine; John C. Richards, M.D., Los Altos; Sally Williams, R.N., M.A., Garden Grove; Sylvia Micik, M.D., San Diego; Dorothy S. Smith, Santa Ana

3:00—Questions and Answers Session

3:30—Position Paper Reactor Panel IV — Santa Ana Room 2

Schools as Community Health Resources

Moderators: Anna Foudy, San Francisco, and Bruno Merz, Burlingame

Position Paper: Thomas McSweeney, Ed.D., San Francisco

Panel Members: John Bishop, M.D., San Diego; Bradford Cohn, M.D., San Francisco; Patricia Lindamood, San Luis Obispo; E. Dean Lovett, M.D., Clearlake Oaks; Helen Rudee, Santa Rosa; Margaret Stephens, M.D., San Francisco

4:30—Questions and Answers Session

SUNDAY, MARCH 11 — Santa Ana Room 1

9:00—

Feedback on Position Papers Relating to Health Education

Moderator: Patricia Hill, M.P.H., Sacramento

9:00— — Santa Ana Room 2

Feedback on Position Papers Relating to Health Services

Moderator: George Cunningham, M.D., Berkeley

9:45—Discussion Periods — Santa Ana Rooms 1 and 2

Health Education and Health Services Groups

11:00—Recess

11:15—Synthesis and Implementation — Santa Ana Rooms 1 and 2

Chairman: B. Otis Cobb, M.D., Woodland

12:00—Luncheon — Anaheim Room

Guest Speaker: H. Glenn Davis, Program Manager, Early Childhood Education, State Department of Education, Sacramento

SUNDAY, MARCH 11 — Magnolia Room C

TREATMENT FOR ALCOHOLISM AND OTHER DRUG ABUSE

Presented jointly by
CMA Committee on Alcoholism
CMA Committee on Dangerous Drugs

Cosponsored by
Orange County Medical Association
Orange County Community Mental Health Services
California Society of Internal Medicine
American Public Health Association

Reservation fee: $10, includes luncheon.

(Please use Reservation Form printed on page 28.)

9:00—Why Are We Here Today?—Alfred Auerback, M.D., San Francisco

9:10—Games We Have Played on Physicians

Moderator: Saul Stolzberg, M.S.W., Santa Ana

Panelists: Arthur Dostrow, M.D., Fullerton; John A. Newsome, M.D., Laguna; Patients and representatives from alcoholism treatment programs, methadone maintenance and a drug-free residential treatment family

10:00—How to Manage a Physician-Patient Relationship with an Alcoholic or Drug Abuser—Karl J. Deissler, M.D., Luzern, Switzerland

Panelists: Stanford B. Rossiter, M.D., Redwood City; Donald F. Taugher, M.D., Monterey

11:00—A Coordinated, Comprehensive, County-Wide Program for the Treatment of the Alcoholic and Drug Abuser —What Does It Look Like? How Does It Work?

Orange County is chosen for the model because it is an example of good coordination among treatment components, good relationships with private physicians, ease of placement, and concern primarily for the patient. Panelists will be administrators, treatment staff, and patients.

Panelists: Ernest J. Klatte, M.D., Santa Ana; John LeValley, M.D., Santa Ana; Daniel Feldman, M.D., Santa Ana, and others

Questions and answers with the audience will be encouraged throughout the morning presentations.

12:00—Luncheon—Realistic Expectations for the Treatment of Alcoholism and Drug Abuse in the United States—An Analysis and Critique of Federal Policy—Roger O. Egeberg, M.D., Special Assistant for Health Policy, Department of HEW, Washington, D.C.

1:30— — Roundtable Discussions

Discussions will be scheduled so that it will be possible to take part in more than one during the afternoon. Participants will be free to move from table to table.

Table 1: **Detoxification—All Forms**—Charles E. Becker, M.D., and Robert Roe, M.D., San Francisco

Table 2: **Treatment of Alcoholism—Acute, Convales**

cing and After-Care—Max Schneider, M.D., Orange; Nicholas J. Khoury, M.D., Los Angeles

Table 3: **Methadone Maintenance**—R. Edward Quass, M.D., Tucson, Arizona; Saul Stolzberg, M.S.W., Santa Ana

Table 4: **Therapeutic Community Programs on Mendocino Family and Synanon Models**—Karl J. Deissler, M.D., Luzern, Switzerland; Michael Takanikos, Santa Ana

Table 5: **Family Counseling about Drug Dependence in the Physician's Office**—Jokichi Takamine, M.D., Los Angeles; Daniel Black, M.D., Castro Valley

Table 6: **Private Practice: Care and Management of Drug Abusers—Acute and On-Going Treatment**—Arthur Dostrow, M.D., Fullerton; Edward Taub, M.D., Orange

Table 7: **Private Practice: Care and Management of Alcoholics—Acute and Ongoing Treatment**—Jack David Gordon, M.D., San Francisco; David Geddes, M.D., Santa Ana

Table 8: **How to Evaluate the Different Forms of Treatment**—Loran Archer, Sacramento; John LeValley, M.D., Santa Ana

Table 9: **What is the Difference Between a Private, Community-Based Program and a County Program? What Is the Role of the Physician in Private Programs?**—Ernest J. Klatte, M.D., Santa Ana; Arthur Bolter, M.D., San Leandro

Table 10: **Legislation Affecting Treatment—Federal, State, Local**—Jess W. Bromley, M.D., San Leandro; Matthew O'Connor, San Francisco

Embassy Room East IV

Films will be shown concurrently with Roundtable Discussions.

1:30—**What Did You Take?**

2:15—**Exploring the Treatment of Alcoholism**

3:00—**Junkies Are People**

3:45—**Glass Houses**

Acceptable for Category 1 Credit under the CMA Certification Program

MONDAY, MARCH 12 — Embassy Room East I

Is Your Practice Ready for Data Processing?

A Conference on Medical Data Processing Systems

Cosponsored by CMA Committee on Insurance and Prepayment, and Health Sciences Data Processing Society

1:00—**Introduction**—Oscar W. Hills, M.D., San Mateo

1:05—**Panel Discussion**—Modern Medical Data Processing Systems: Advantages and Problems

Panelists: William C. Clauer, Van Nuys; William A. Harding, Millbrae; Ronald Morgan, Burlingame

2:00—**Questions and Answers Sessions**

make reservations now and plan to attend . . .

CMA PRESIDENTS' DINNER

Sunday evening, March 11

Disneyland Hotel, Anaheim

Dinner will be at 7:30 p.m., immediately following the traditional Presidents' Reception at the CMA Annual Session, and the leaders of the CMA and the Woman's Auxiliary to the CMA will be honored. The dinner will feature live music, entertainment, and awards and presentations formerly made during the House of Delegates sessions.

Tickets are $10.50 each. Tables seat 10 persons. For reservations, send check made out to WA-CMA to: Woman's Auxiliary to CMA, 10161 Broadview Place, Santa Ana 92705.

ALLERGY

Chairman.....HAROLD S. NOVEY, M.D., Whittier
Secretary.....J. GARLAND STROUP, M.D., Sacramento
Assistant Secretary.....JULIAN L. HARWELL, M.D., Pasadena

SATURDAY, MARCH 10 — Magnolia Room D

Recent Advances in Allergy and Clinical Immunology

Cosponsored by the California Society of Allergy

Moderator: J. Garland Stroup, M.D., Sacramento

8:50—Introductory Remarks—Harold S. Novey, M.D., Whittier

9:00—Newer Methods of Evaluating Allergic Reactivity—Oscar Lee Frick, M.D., San Francisco

9:30—Laboratory Evaluation of the Immune Deficient Patient—Arthur J. Ammann, M.D., San Francisco

10:00—Questions and Answers Session

10:15—Recess

10:30—Epidemiology of Asthma—John E. Salvaggio, M.D., New Orleans

11:15—Recent Studies of Hypersensitivity Lung Disease—Vincent A. Marinkovich, M.D., Stanford

11:45—Questions and Answers Session

12:00—Luncheon and business meeting with the California Society of Allergy

Moderator: Julian L. Harwell, M.D., Pasadena

2:00—Panel on Current Status of Studies in Food Allergy and Food Hypersensitivity—William C. Deamer, M.D., San Francisco; Douglas C. Heiner, M.D., Torrance

3:00—Questions and Answers Session

Reports from Allergy Trainees on Current Research in Allergy

3:15—Long-Term Study on Use of a Beta-2 Stimulator (Terbutoline®) in Treatment of Asthma—Paul Cloninger, M.D., Irvine

3:30—Long-Term Study on Use of Cromolyn Sodium (Intal®) in Treatment of Asthma—Allan Giannini, M.D., San Francisco

3:45—Tissue Monitoring of Arterial Blood Oxygen in Children with Asthma—Richard Davis, M.D., Irvine

4:00—The Importance of the House Dust Mite and House Dust in Southern California—Loula Amin, M.D., Irvine

4:15—The Correlation of Penicillin Hypersensitivity with Skin Testing and Histamine Release from Rat Mast Cells—Anthony Hirsch, M.D., Los Angeles

4:30—Questions and Answers Session

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5:30—Social Hour—Members, Wives, and Guests of the California Society of Allergy

ANESTHESIOLOGY

Chairman.....ERIC WEBB, M.D., Los Angeles
Secretary.....JOHN C. DAMRON, M.D., Palo Alto
Assistant Secretary.....EDWIN H. LEWIS, M.D., San Diego

SUNDAY, MARCH 11 — Embassy Room West III

MORNING SESSION

Joint Meeting of the Sections on Anesthesiology and Otolaryngology

Cosponsored by Stanford University School of Medicine, Department of Anesthesiology

Acute Airway Problems in Infants and Children

9:00—Panel Discussion

Moderator: John Tucker, M.D., Philadelphia

Panel Members and Topics:

Intubation vs. Tracheostomy—Alvin Hackel, M.D., Stanford

Local, Topical or General Anesthesia—Seymour Cohen M.D., Los Angeles

Post-Intubation Care—Kevin Wheaton, M.D., Palo Alto

Tracheostomy: Technique and Complications—Tom Miller, M.D., Oakland

10:30—Recess

11:00—Clinical Manifestations of Congenital Anomalies of the Larynx—John Tucker, M.D., Philadelphia

12:00—Luncheon break

Acceptable for Category 1 Credit under the CMA Certification Program

Afternoon Session

1:30—Electrical Hazards in the Operating Room—Delmar Snider, M.D., Stanford

2:30—Acupuncture—James Rhee, M.D., Oakland

3:30—Business Meeting

CHEST DISEASES

Chairman.....Angelo M. May, M.D., San Francisco
Secretary.....Oscar Balchum, M.D., Los Angeles
Assistant Secretary.....Wilbur Hallett, M.D., Burbank

SUNDAY, MARCH 11 Magnolia Room B

9:00—Business Meeting and Election of Officers

Joint Meeting

Sections on Chest Diseases and Internal Medicine

Cosponsored by California Society of Internal Medicine; California Thoracic Society; American College of Chest Physicians, California Chapter

Chairmen: Angelo M. May, M.D., San Francisco; Daniel W. Black, M.D., Castro Valley

9:15—Valvular Surgery: When Should It and When Should It Not Be Recommended?—Eliot Corday, M.D., Los Angeles

9:40—The Role of Coronary Cineangiography in Valvular Surgery—Melvin P. Judkins, M.D., Loma Linda

10:05—Valvular Surgery and Simultaneous Coronary Revascularization—Ellsworth Wareham, M.D., Loma Linda

10:30—Break

10:40—Aortic Valve Surgery—Jack M. Matloff, M.D., Los Angeles

11:05—Results in the Use of the Wada Valve—Juro Wada, M.D., Sapporo, Japan

11:30—Discussion Period

12:00—Luncheon

12:30—Luncheon Address: Valvular Surgery—Albert Starr, M.D., Portland, Oregon

(Advance reservation and payment, $7.50, is required for luncheon. Please use Reservation Form printed on page 28.)

Acceptable for Category 1 Credit under the CMA Certification Program

Joint Meeting

Sections on Chest Diseases and Industrial Medicine and Surgery; and Western Industrial Medical Association

Cosponsored by California Thoracic Society and American College of Chest Physicians, California Chapter

Pulmonary Diseases of Occupational Origin

Chairmen: Hans E. Einstein, M.D., Bakersfield; Anthony A. Mira, M.D., Santa Monica

2:00—Introduction: Delineation of the Problem—Jean S. Felton, M.D., Los Angeles

2:05—Black Lung

Radiological Aspects—E. N. Sargent, M.D., Los Angeles

Clinical Aspects—James Theodore, M.D., Stanford

Research and Other Aspects—LeRoy Lapp, M.D., Morgantown, West Virginia

2:35—Asbestosis—I. J. Selikoff, M.D., New York City

3:05—Questions and Answers

3:15—Recess

3:30—Panel Discussion—Jean S. Felton, M.D., Los Angeles, *Moderator*

Broncho-Pulmonary Reactions to Molds and Fungi—Oscar J. Balchum, M.D., Ph.D., Los Angeles

Pulmonary Reaction to Plastics, Metals and Other Materials of Industrial Origin—John R. Goldsmith, M.D., Berkeley

Response: Subjecting Workers to These Hazards—George H. R. Taylor, AFL-CIO, Washington, D.C.

4:15—Questions and Answers

Acceptable for Category 1 Credit under the CMA Certification Program

DERMATOLOGY

Chairman.....William M. Gould, M.D., Stanford
Secretary.....T. Richard Mihan, M.D., Los Angeles
Assistant Secretary.....Ellis Mitchell, M.D., Greenbrae

SUNDAY, MARCH 11 Embassy Room East IV

Symposium

Cosponsored by Los Angeles Dermatological Society, Metropolitan Dermatological Society, Orange County Dermatological Society, and Department of Dermatology, University of California, Irvine, California College of Medicine

Tomorrow Is Here Today and To Stay—The Dermatologist and Continuing Medical Education, Medical Monitoring and Mountains of Medical Insurance

Chairman: William M. Gould, M.D., Stanford

8:30—The Role of the State Board of Medical Examiners in Protecting the Consumer—Tirso del Junco, M.D., Los Angeles

9:00—Medical Claims Processing—Jack Byrne, Director of Professional Relations, Medicare Administration, Occidental Life Insurance Co., Los Angeles

9:30—**The Role of A Self-Assessment Program in Continuing Medical Education**—Victor Newcomer, M.D., Los Angeles

10:00—**Recess**

10:15—**Histopathologists' Panel Discussion: Common Histopathologic Problems with which the Clinician Gifts the Dermal Histopathologist**—Moderator: Robert I. Freedman, M.D., Downey

Problems of Biopsy—Paul Hirsch, M.D., Beverly Hills

The Clinician and Pathologic Diagnosis—Bernard Gottlieb, M.D., San Bernardino

Histopathologic Surprises (Eye Openers)—Louis H. Winer, M.D., Beverly Hills

Common Errors in Interpretation of Skin Slides—Leo Indianer, M.D., Encino

The Dermatologist Looks at the Umbilicus—Leo Kaplan, M.D., Los Angeles

11:15—**Insuring Quality Health Care: A Legislator's Viewpoint**—Assemblyman Gordon Duffy, Member of the Assembly, Twenty-first Assembly District

11:45—**Leprosy in a Large General Hospital**—Thomas H. Rea, M.D., Downey

12:15—**Panel Discussion**—Moderator: T. Richard Mihan, M.D., Los Angeles

The Difference between the Desire and the Need for Health Care—Norman Levan, M.D., Los Angeles

Town or Gown Medicine—How to Bring Them Together for the Patients' Benefit—Edwin T. Wright, M.D., Los Angeles

The Relationship of the Private Practitioner to the University Center—John H. Epstein, M.D., San Francisco

The Role of Dermatologic Training Centers in Quality Health Care—Ronald M. Reisner, M.D., Los Angeles

Acceptable for Category 1 Credit under the CMA Certification Program

12:55—**Business Meeting**

GENERAL AND FAMILY PRACTICE

Chairman.....A. J. Wyatt, M.D., Anaheim
Secretary.....Peter J. Kistler, M.D., San Bruno
Assistant Secretary.....Holger Rasmussen, M.D., Fremont

SATURDAY, MARCH 10 **Embassy Room West I**

Cosponsored by University of California, Irvine, California College of Medicine

Chairman: Arthur J. Wyatt, M.D., Anaheim

Moderator: J. Blair Pace, M.D., Irvine

8:00—**Welcome**—Arthur J. Wyatt, M.D., Anaheim

8:15—**Government Administered Medicine: Possible?, Probable?, Preventable?**—David Allan, M.D., San Diego

9:15—**Foundations as an Alternative Method of Medical Practice**—Donald Harrington, M.D., Stockton

10:15—**PAS-MAP: Committee Hospital Peer Review Through Educational Efficiency, Not Committee Meetings**—Robert Brittain, M.D., Denver

11:15—**How to Use the Problem-Oriented Concept in Practice**—Harold Cross, M.D., Hampden Highlands, Maine

1:00—**Luncheon break**

2:00—**Panel Discussion: America's Medical Future**—Drs. Allan Brittain, Cross and Harrington—Moderator: John F Bridgeman, M.D., Orange

Acceptable for Category 1 Credit under the CMA Certification Program

This meeting has been made possible through grants in-aid from GEIGY Pharmaceuticals; The Upjohn Company; Pharmaceuticals Division CIBA-GEIGY Corporation; Merck, Sharp & Dohme; Ayerst Laboratories; National Foundation-March of Dimes; Roche Laboratories

4:00—**Business meeting**

SUNDAY, MARCH 11 **Magnolia Room 1**

Joint Meeting of the Sections on Plastic Surgery an General and Family Practice

Cosponsored by Stanford University School of Medicin and the University of California, San Francisco, Scho of Medicine

9:00—**Aesthetic Surgery: Its Growth and Development**—Sa vador Castanares, M.D., Los Angeles

9:30—**Plastic Surgery for the General Practitioner**—Panel Di cussion by the Stanford University Group

Chairman: Donald R. Laub, M.D., Stanford

Plastic Surgery Appropriate for the General Pract tioner—Lars M. Vistnes, M.D., Stanford

Plastic Surgery Appropriate for the General Pract tioner with Special Training—Mar McGregor, M.I Stanford

Plastic Surgery Usually Referred to a Specialist—Er est N. Kaplan, M.D., Stanford

Plastic Surgery from the General Practitioner's Vie point—Paul Daines, M.D., Montpelier, Idaho

12:00—**Luncheon break**

2:00—**Tissue Transplantation by Microvascular Technique Reconstructive Surgery: Experimental and Clinical A plications**—Harry J. Buncke, Jr., M.D., San Mateo; C *authors:* Donald McClean, M.D., Oakland; Phillip Geor M.D., San Francisco; George Commons, M.D., Sa Clara; Bernard Creech, M.D., San Francisco.

2:45—The Crippled Hand—Types and Management

1. Burns and Contractions
2. Spastic Hands
3. Paralyzed Hands
4. Crush and Amputations
5. Rheumatoids

Discussants: William P. Byrnes, M.D., San Francisco; Donald J. Mangus, M.D., Chico; Walter J. Treanor, M.D., San Francisco.

Acceptable for Category 1 Credit under the CMA Certification Program

GENERAL SURGERY

Chairman.....John E. Connolly, M.D., Irvine
Secretary.....Albert D. Hall, M.D., San Francisco
Assistant Secretary....David B. Hinshaw, M.D., Loma Linda

MONDAY, MARCH 12 — Magnolia Room B

Cosponsored by American College of Surgeons, Northern and Southern California Chapters

12:00—Luncheon Meeting: Jointly with American College of Surgeons, Northern and Southern California Chapters —Presiding: John E. Connolly, M.D., Irvine

12:45—Luncheon Address: Physiological Basis for Peptic Ulcer Surgery—Edward R. Woodward, M.D., Gainesville, Fla.

1:20—Peptic Ulcer Surgery—Panel Discussion

Vagotomy—Truncal Selective or Superselective?

"Combined Operations"—What Is Their Role?

Emergency Operations

Long-Term Results—Whose To Believe?

Post-Operative Sequelae

Moderator: David B. Hinshaw, M.D., Loma Linda

Members of the Panel: Edward R. Woodward, M.D., Gainesville, Florida; Edward A. Stemmer, M.D., Long Beach; Edward P. Passaro, Jr., M.D., Los Angeles

2:30—Recess

2:45—Calcium and Gastric Secretions—Edward P. Passaro, Jr., M.D., Los Angeles

3:05—Intestinal Ischemia: Diagnosis and Surgical Management—Edward A. Stemmer, M.D., Long Beach

3:25—Hiatus Hernia—Edward R. Woodward, M.D., Gainesville, Florida

3:50—Questions and Discussion

4:00—Carcinoma of the Breast: Therapeutic Controversy—Arthur J. Donovan, M.D., Los Angeles

4:25—Questions and Discussion

4:35—Recess

Acceptable for Category 1 Credit under the CMA Certification Program

4:45—Business Meeting

INDUSTRIAL MEDICINE AND SURGERY

Chairman.....Francis R. Schwartz, M.D., San Francisco
Secretary.....Anthony A. Mira, M.D., Santa Monica
Assistant Secretary.....John E. Meyers, M.D., San Jose

SUNDAY, MARCH 11 — Magnolia Room B

Joint Meeting

Sections on Industrial Medicine and Surgery and Chest Diseases; and Western Industrial Medical Association

Cosponsored by the California Thoracic Society and the American College of Chest Physicians, California Chapter

Pulmonary Diseases of Occupational Origin

Chairmen: Hans E. Einstein, M.D., Bakersfield; Anthony A. Mira, M.D., Santa Monica

1:30—Business Meeting, Section on Industrial Medicine and Surgery—Francis R. Schwartz, M.D., San Francisco, presiding

2:00—Introduction: Delineation of the Problem—Jean S. Felton, M.D., Los Angeles

2:05—Black Lung

Radiological Aspects—E. N. Sargent, M.D., Los Angeles

Clinical Aspects—James Theodore, M.D., Stanford

Research and Other Aspects—LeRoy Lapp, M.D., Morgantown, West Virginia

2:35—Asbestosis—I. J. Selikoff, M.D., New York City

3:05—Questions and Answers

3:15—Recess

3:30—Panel Discussion—Jean S. Felton, M.D., Los Angeles, *Moderator*

Broncho-Pulmonary Reactions to Molds and Fungi—Oscar J. Balchum, M.D., Ph.D., Los Angeles

Pulmonary Reactions to Plastics, Metals and other Materials of Industrial Origin—John R. Goldsmith, M.D., Berkeley

Response: Subjecting Workers to These Hazards—George H. R. Taylor, AFL-CIO, Washington, D.C.

4:15—Questions and Answers

Acceptable for Category 1 Credit under the CMA Certification Program

INTERNAL MEDICINE

Chairman Daniel W. Black, M.D., Castro Valley
Secretary Augustus Stiegler, M.D., San Francisco
Assistant Secretary Ernest Pund, Jr., M.D., La Jolla

SUNDAY, MARCH 11 — Magnolia Room B

9:00—**Business Meeting,** Section on Internal Medicine

Joint Meeting

Sections on Internal Medicine and Chest Diseases

Cosponsored by California Society of Internal Medicine, California Thoracic Society and the American College of Chest Physicians, California Chapter

Chairmen: Angelo M. May, M.D., San Francisco; Daniel W. Black, M.D., Castro Valley

9:15—**Valvular Surgery: When Should It and When Should It Not Be Recommended?**—Eliot Corday, M.D., Los Angeles

9:40—**The Role of Coronary Cineangiography in Valvular Surgery**—Melvin P. Judkins, M.D., Loma Linda

10:05—**Valvular Surgery and Simultaneous Coronary Revascularization**—Ellsworth Wareham, M.D., Loma Linda

10:30—**Break**

10:40—**Aortic Valve Surgery**—Jack M. Matloff, M.D., Los Angeles

11:05—**Results in the Use of the Wada Valve**—Juro Wada, M.D., Sapporo, Japan

11:30—**Discussion Period**

12:00—**Luncheon**

12:30—**Luncheon Address: Valvular Surgery**—Albert Starr, M.D., Portland, Oregon

(Advance reservation and payment, $7.50, is required for luncheon. Please use Reservation Form on page 28.)

Acceptable for Category 1 Credit under the CMA Certification Program

NEUROLOGY

Chairman J. Carroll Ramseyer, M.D., Los Angeles
Secretary Edward H. Davis, M.D., Beverly Hills
Assistant Secretary Edward E. Shev, M.D., San Francisco

SUNDAY, MARCH 11 — Magnolia Room A

Joint meeting of the Sections on Neurology and Otolaryngology

The Diagnosis and Management of the Dizzy Patient

1:30—Panel Discussion

Moderator: Robert 1. Kohut, M.D., Irvine

Panel Members and Topics:

The Historical and Physical Examination of the Dizzy Patient—Edward H. Davis, M.D., Beverly Hills

Vertigo of Peripheral or VIII Nerve Origin: Diseases and Diagnostic Tests—Jack Lee Pulec, M.D., Los Angeles

The Otoneurological Workup: Past, Present and Future—H. Ronald Konrad, M.D., Torrance

Vertigo of Central Origin: Diseases and Diagnostic Tests—James H. Nelson, M.D., San Diego

3:15—**Break**

3:30—**Business Meeting,** Section on Neurology

OBSTETRICS AND GYNECOLOGY

Chairman Alan J. Margolis, M.D., San Francisco
Secretary William F. Kroener, Jr., M.D., Whittier
Assistant Secretary Charles Weber, M.D., La Jolla

MONDAY, MARCH 12 — Magnolia Room C

Morning Session

Joint Meeting of the Sections on Obstetrics and Gynecology, and Urology

Cosponsored by California Section, District 8, American College of Obstetricians and Gynecologists

Chairman: Charles Weber, M.D., La Jolla

9:00—**Urinary Stress Incontinence**

Moderator: James H. McClure, M.D., Irvine

Speakers: Thomas B. Lebherz, M.D., Los Angeles; Jack R. Robertson, M.D., Santa Maria; Emil A. Tanagho, M.D., San Francisco; Sherwin D. Lewis, M.D., Torrance

11:00—**Coffee break**

11:15—**Operative Infusion Pyelography in Pelvic Surgery**—Charles F. Wright, M.D., La Jolla; Charles G. Campbell, M.D., La Jolla; Frank J. Mullett, R.T., C.R.T., La Jolla

12:00—**Luncheon** and Combined Meeting with District 8, American College of Obstetricians and Gynecologists

Normal and Abnormal Sexual Differentiation and Virilization—Paul C. MacDonald, M.D., Dallas

2:00—**Break**

Afternoon Session

2:15—**Clinical Application of Genetic Detection and Counseling**—Kurt Benirschke, M.D., La Jolla

3:00—**Break**

3:15—**Panel Discussion on Gynecological Endocrinology**

Moderator: Daniel Mishell Jr., M.D., Los Angeles

Speakers: Howard L. Judd, M.D., La Jolla; Val Davajan, MD., Los Angeles; Hans Simmer, M.D., Los

Angeles; Ronald M. Nelson, M.D., Loma Linda; W. Leslie G. Quinlivan, M.D., Irvine

Acceptable for Category 1 Credit under the CMA Certification Program

5:00—Business Meeting

OPHTHALMOLOGY

Chairman Rush M. Blodget, Jr., M.D., Redding
Secretary John A. Berg, M.D., Sacramento
Assistant Secretary ..Robert Christensen, M.D., Los Angeles

SATURDAY, MARCH 10 2525 DuPont Drive, Irvine*

1:00 to 4:30 **Conference on Ocular Therapeutics**

Co-sponsored by University of California, Irvine, California College of Medicine

Moderator: Irving Leopold, M.D., New York City

Acceptable for Category 1 Credit under the CMA Certification Program

This program was made possible in part by a grant-in-aid from Allergan Pharmaceutical

*Transportation will be available from the Disneyland Hotel (Monorail Station) at 12:30 p.m.

SUNDAY, MARCH 11 Embassy Room East V

Strabismus Conference

Cosponsored by University of California, Irvine, California College of Medicine

Chairman: Rush M. Blodget, Jr., Redding

Morning Session

Moderator: Joseph G. Tirico, M.D., Orange

9:00—**Introduction**—Rush M. Blodget, Jr., M.D., Redding

9:10—**Congenital Esotropia Management**—Eugene R. Folk, M.D., Skokie, Illinois

9:40—**Management of Overcorrection and Undercorrection of Esotropia**—Richard L. Elliott, M.D., Santa Ana

10:10—**Intermittent Exotropia Management**—Philip C. Diorio, M.D., Torrance

10:40—**Recess**

10:50—**Management of Exotropia Overcorrection**—George L. Tabor, M.D., San Diego

11:20—**Superior Oblique Muscle Surgery**—Arthur J. Jampolsky, M.D., San Francisco

11:50—**Business Meeting**

12:15—**Luncheon**—Robert Christensen, M.D., Los Angeles, *Toastmaster*

Afternoon Session

Moderator: John A. Berg, M.D., Sacramento

2:00—**Inferior Oblique Surgery**—Eugene R. Folk, M.D., Skokie, Illinois

2:30—**Nystagmus: Surgical Management**—Robert M. Sinskey, M.D., Santa Monica

3:00—**Recess**

3:15—**Special Eye Muscle Syndromes Management**—Alan B. Scott, M.D., San Francisco

3:45—**Paralytic Esotropia Management: Congenital and Post-Traumatic**—Stephen S. Seiff, M.D., Beverly Hills

4:15—**Question and Answer Period**

Acceptable for Category 1 Credit under the CMA Certification Program

ORTHOPEDICS

Chairman John V. Banta, M.D., San Diego
Secretary Michael Shlens, M.D., Los Angeles
Assistant Secretary Brack Davis, M.D., Roseville

TUESDAY, MARCH 13 Embassy Rooms West I and II

Joint Meeting of the Sections on Orthopedics, Pediatrics, and Radiology

Cosponsored by the American Academy of Pediatrics, California Chapter II

Recognition and Treatment of Common Pediatric Orthopedic Problems

Chairmen: John V. Banta, M.D., San Diego
Gabriel H. Wilson, M.D., Los Angeles
J. Harold Batzle, M.D., Riverside

2:00—**Treatment of Forearm Fractures in Children**—Walter Blount, M.D., Milwaukee

3:00—**Iatrogenic Problems in the Management of Children's Orthopedics**—G. Wilbur Westin, M.D., Los Angeles

3:30—**Recognition of the Battered Child**—Frederick N. Silverman, M.D., Cincinnati

4:00—**Interesting Bone Lesions in Children**—John L. Gwinn, M.D., Los Angeles

4:30—**Questions and Answers with Speakers' Panel**

Acceptable for Category 1 Credit under the CMA Certification Program

5:10—**Annual Meeting**, Section on Orthopedics

OTOLARYNGOLOGY

Chairman Paul H. Ward, M.D., Los Angeles
Secretary Richard Goode, M.D., Stanford
Assistant Secretary William Simpson, M.D., Los Angeles

SUNDAY, MARCH 11 **Embassy Room West III**

Morning Session

Joint Meeting of the Sections on Otolaryngology and Anesthesiology

Cosponsored by Stanford University School of Medicine

Acute Airway Problems in Infants and Children

9:00—**Panel Discussion**

Moderator: John Tucker, M.D., Philadelphia

Panel Members and Topics:

Intubation vs. Tracheostomy—Alvin Hackel, M.D., Stanford

Local, Topical or General Anesthesia—Seymour Cohen, M.D., Los Angeles

Post-Intubation Care—Kevin Wheaton, M.D., Palo Alto

Tracheostomy: Technique and Complications—Tom Miller, M.D., Oakland

10:30—**Recess**

11:00—**Clinical Manifestations of Congenital Anomalies of the Larynx**—John Tucker, M.D., Philadelphia

12:00—**Luncheon break**

Acceptable for Category 1 Credit under the CMA Certification Program

Magnolia Room A

Afternoon Session

Joint Meeting of the Sections on Otolaryngology and Neurology

The Diagnosis and Management of the Dizzy Patient

1:30—Panel Discussion

Moderator: Robert I. Kohut, M.D., Irvine

Panel Members and Topics:

The Historical and Physical Examination of the Dizzy Patient—Edward H. Davis, M.D., Beverly Hills

Vertigo of Peripheral or VIII Nerve Origin: Diseases and Diagnostic Tests—Jack Lee Pulec, M.D., Los Angeles

The Otoneurological Workup: Past, Present and Future—H. Ronald Konrad, M.D., Torrance

Vertigo of Central Origin: Diseases and Diagnostic Tests—James H. Nelson, M.D., San Diego

3:15—**Break**

3:30—**Business Meeting, Otolaryngology Section**

PATHOLOGY

Chairman Robert S. Cox, Jr., M.D., San Jose
Secretary David Korn, M.D., Stanford
Assistant Secretary Phillips L. Gausewitz, M.D., La Jolla

SATURDAY, MARCH 10 **Embassy Room West III**

9:00—**Transfusion Therapy in Surgical Patients**—Victor Richards, M.D., San Francisco

9:25—**The Use of Blood Components**—David Borucki, M.D., Carmel

9:50—**Coffee Break**—Sponsored by California Society of Pathologists

10:15—**Therapy of Hemorrhagic Disorders**—Carol Kasper, M.D., Los Angeles

10:40—**What Every Clinician Should Know about the Operation of a Blood Bank but Is Afraid to Ask**—Byron Myhre, M.D., Ph.D., Torrance

11:05—**Questions of Panelists**

12:00—**Business Meeting**

SUNDAY, MARCH 11 **Embassy Rooms West I and II**

California Tumor Tissue Registry
Pathology Conference

Pigmented and Other Tumors of the Skin

Sponsored by the American Cancer Society, California Division; and the University of Southern California School of Medicine

Acceptable for Category 1 Credit under the CMA Certification Program

(See page 13 for registration information.)

PEDIATRICS

Chairman J. Harold Batzle, M.D., Riverside
Secretary Frederick A. Frye, M.D., San Diego
Assistant Secretary Leon P. Smith, M.D., Mill Valley

TUESDAY, MARCH 13 **Embassy Room West I**

Drug Ecology

Cosponsored by the American Academy of Pediatrics, California Chapter II

9:00—**Welcome**—J. Harold Batzle, M.D., Riverside

9:05—**Some Aspects of Drug Pharmacology and Reactions**—Alan K. Done, M.D., Washington, D.C.

9:45—**Vicious Relay: Pregnant Mother—Medication—Unborn Infant**—Edward J. Quilligan, M.D., Los Angeles

10:20—**Intermission**

10:45—**Antivirals in Pediatrics?**—J. J. Quilligan, M.D., Loma Linda

:20—Antibiotics in Pediatrics—Alan K. Done, M.D., Washington, D.C.

:15—Luncheon and Questions and Answers Session

Acceptable for Category 1 Credit under the CMA Certification Program

:45—Annual Meeting, Section on Pediatrics

If you plan to attend the luncheon, please send your name and address with a check for $5.50 (payable to Leon P. Smith, M.D.) to Doctor Smith at 141 Camino Alto, Mill Valley 94941.

Embassy Rooms West I and II

Joint Meeting of the Sections on Pediatrics, Orthopedics, and Radiology

Cosponsored by the American Academy of Pediatrics, California Chapter II

Recognition and Treatment of Common Pediatric Orthopedic Problems

Chairmen: J. Harold Batzle, M.D., Riverside; John V. Banta, M.D., San Diego; Gabriel H. Wilson, M.D., Los Angeles

2:00—Treatment of Forearm Fractures in Children—Walter Blount, M.D., Milwaukee

3:00—Iatrogenic Problems in the Management of Children's Orthopedics—G. Wilbur Westin, M.D., Los Angeles

3:30—Recognition of the Battered Child—Frederick N. Silverman, M.D., Cincinnati

4:00—Interesting Bone Lesions in Children—John L. Gwinn, M.D., Los Angeles

4:30—Questions and Answers with Speakers' Panel

Acceptable for Category 1 Credit under the CMA Certification Program

PHYSICAL MEDICINE AND REHABILITATION

Chairman Carrie E. Chapman, M.D., Los Angeles
Secretary.....W. Harvey Moore, M.D., San Leandro
Assistant Secretary....Seth H. Douthett, M.D., Long Beach

SATURDAY, MARCH 10 — Pacific Room

2:00—Introductory Remarks—Carrie E. Chapman, M.D., Los Angeles

Moderator: Seth H. Douthett, M.D., Long Beach

2:10—Physiologic and Pathologic Changes in Cerebrovascular Accidents—Jerome Gersten, M.D., Denver

2:30—Rehabilitation Prognosis—Jerome Gersten, M.D., Denver

3:00—Current Bracing Concepts—Bernard J. Michela, M.D., Long Beach

3:15—Recess

3:30—Reconstructive Surgery in Hemiplegia—Francis Thornton, M.D., Long Beach

3:50—Speech Therapy—Elizabeth Wallace, M.A., Costa Mesa

4:10—Post-Hospitalization Management—Bernard J. Michela, M.D., Long Beach

4:30—Question and Answer Period

4:50—Business Meeting

PLASTIC SURGERY

Chairman.....Raymond R. Kauffman, M.D., Burlingame
Secretary.....E. C. Brown, M.D., San Francisco
Assistant Secretary
.....Roger P. Friedenthal, M.D., San Francisco

SUNDAY, MARCH 11 — Magnolia Room D

Joint Meeting of the Sections on Plastic Surgery and General and Family Practice

Cosponsored by the Stanford University School of Medicine and University of California, San Francisco, School of Medicine

9:00—Aesthetic Surgery: Its Growth and Development—Salvador Castanares, M.D., Los Angeles

9:30—Plastic Surgery for the General Practitioner—Panel Discussion by the Stanford University Group

Chairman: Donald R. Laub, M.D., Stanford

Plastic Surgery Appropriate for the General Practitioner—Lars M. Vistnes, M.D., Stanford

Plastic Surgery Appropriate for the General Practitioner with Special Training—Mar McGregor, M.D., Stanford

Plastic Surgery Usually Referred to a Specialist—Ernest N. Kaplan, M.D., Stanford

Plastic Surgery from the General Practitioner's Viewpoint—Paul Daines, M.D., Montpelier, Idaho

12:00—Luncheon break

2:00—**Tissue Transplantation by Microvascular Technique for Reconstructive Surgery: Experimental and Clinical Applications**—Harry J. Buncke, Jr., M.D., San Mateo

Co-authors: Donald McClean, M.D., Oakland; Phillip George, M.D., San Francisco; George Commons, M.D., Santa Clara; Bernard Creech, M.D., San Francisco

2:45—**The Crippled Hand—Types and Management**

1. Burns and Contractions
2. Spastic Hands
3. Paralyzed Hands
4. Crush and Amputations
5. Rheumatoids

Discussants: William P. Byrnes, M.D., San Francisco; Donald J. Mangus, M.D., Chico; Walter J. Treanor, M.D., San Francisco

Acceptable for Category 1 Credit under the CMA Certification Program

4:45—**Business Meeting**—Section on Plastic Surgery

PREVENTIVE MEDICINE AND PUBLIC HEALTH

Chairman.....RICHARD H. SVIHUS, M.D., Santa Cruz
Secretary.....DONALD G. RAMRAS, M.D., San Diego
Assistant Secretary....JAMES T. HARRISON, M.D., Sacramento

MONDAY, MARCH 12 — Magnolia Room D

SYMPOSIUM

Prevention vs. Treatment for Coronary Heart Disease (Primary Prevention by Alteration of Risk Factors vs. Early Intensive Treatment of Patients)

Cosponsored by University of California, Los Angeles, School of Medicine

Chairman: Donald G. Ramras, M.D., San Diego

Moderator: Lester Breslow, M.D., Los Angeles

8:30—**Part I.** David H. Blankenhorn, M.D., Los Angeles; Nemat O. Borhani, M.D., Davis

9:30—**Break**

10:00—**Part II.** Eliot Corday, M.D., Los Angeles; John M. Chapman, M.D., Los Angeles

11:00—**Question Period**

11:30—**Business Meeting**

11:45—**Luncheon Break**

Preventive Medicine—Current Guides for the Practitioner

Moderator: Donald G. Ramras, M.D., San Diego

1:30—**The Latest Treatment Regime for Gonorrhea and Syphilis**—Warren Ketterer, M.D., California State Department of Public Health

2:00—**Commercial Office Laboratory Tests for Gonorrhea: Their Uses and Pitfalls**—Ronald M. Wood, Ph.D., California State Department of Public Health

2:30—**Current Antibiotic Treatment for Tuberculosis**—Kenneth Moser, M.D., San Diego

3:00—**Break**

3:30—**Current Status of Mumps Immunization and Zoster-Immune-Globulin**—James Chin, M.D., California State Department of Public Health

4:00—**Immunization and Health Recommendations for Foreign Travel**—Ronald R. Roberto, M.D., California State Department of Public Health

Acceptable for Category 1 Credit under the CMA Certification Program

PSYCHIATRY

Chairman NORMAN I. GRAFF, M.D., San Mateo
Secretary JOHN S. PECK, M.D., Los Angeles
Assistant Secretary.....HARVEY SMALL, M.D., San Mateo

SUNDAY, MARCH 11 — Embassy Room East VI

Changing Sexual Standards—What Is Normal?

9:00—Society's standards for sexual behavior seem to be undergoing changes in many directions. The panel will discuss these changes from several points of view, and try to deal with the question of how we judge our patients' sexual behavior. Audience participation will be encouraged.

Panel Discussion: Marcia Kraft Goin, M.D., Los Angeles; Martin Grotjohn, M.D., Beverly Hills; Ernest G. Masler, M.D., Sherman Oaks, Jaqueline B. McCandless, M.D., Sherman Oaks; Ralph D. Yaney M.D., Beverly Hills

12:00—**Luncheon Break**

Group Therapy in 1973

Cosponsored by the Los Angeles Group Psychotherapy Society

2:00—**Experience with Group Therapy in Private Practice**—Peter D. King, M.D., Encino

2:30—**The Training of Group Leaders: Who Is Qualified?**—E. Mansell Pattison, M.D., Irvine

3:00—**The Varieties of Group Experience**—Tracey H. McCarley, M.D., Sherman Oaks

3:30—**Panel Discussion and Audience Questions**

4:30—**Business Meeting**

RADIOLOGY

hairman.....GABRIEL H. WILSON, M.D., Los Angeles
ecretary.....ROBERT H. REID, M.D., Los Gatos
ssistant Secretary...DUANE E. BLICKENSTAFF, M.D., La Jolla

UESDAY, MARCH 13 **Embassy Rooms West I and II**

Joint Meeting of the Sections on Radiology, Pediatrics, and Orthopedics

Cosponsored by the American Academy of Pediatrics, California Chapter II

Recognition and Treatment of Common Pediatric Orthopedic Problems

Chairmen: Gabriel H. Wilson, M.D., Los Angeles; J. Harold Batzle, M.D., Riverside; John V. Banta, M.D., San Diego

2:00—**Treatment of Forearm Fractures in Children**—Walter Blount, M.D., Milwaukee

3:00—**Iatrogenic Problems in the Management of Children's Orthopedics**—G. Wilbur Westin, M.D., Los Angeles

3:30—**Recognition of the Battered Child**—Frederick N. Silverman, M.D., Cincinnati

4:00—**Interesting Bone Lesions in Children**—John L. Gwinn, M.D., Los Angeles

4:30—**Questions and Answers, with Speakers' Panel**

Acceptable for Category 1 Credit under the CMA Certification Program

5:10—**Annual Meeting, Section on Radiology**

UROLOGY

Chairman.....STANLEY BROSMAN, M.D., Torrance
Secretary.....PATRICK H. MCLIN, M.D., San Rafael
Assistant Secretary.....JAMES ROHN, M.D., Visalia

MONDAY, MARCH 12 **Magnolia Room C**

Morning Session

Joint Meeting of the Sections on Urology and Obstetrics and Gynecology

Chairman: Charles Weber, M.D., La Jolla

9:00—**Urinary Stress Incontinence**

Moderator: James H. McClure, M.D., Irvine

Speakers: Thomas B. Lebherz, M.D., Los Angeles; Jack R. Robertson, M.D., Santa Maria; Emil A. Tanagho, M.D., San Francisco; Sherwin D. Lewis, M.D., Torrance

11:00—**Coffee break**

11:15—**Operative Infusion Pyelography in Pelvic Surgery**—Charles F. Wright, M.D., La Jolla; Charles G. Campbell, M.D., La Jolla; Frank J. Mullett, R.T., C.R.T., La Jolla

12:00—**Luncheon** and Combined Meeting with District 8, American College of Obstetricians and Gynecologists

Normal and Abnormal Sexual Differentiation and Virilization—Paul C. MacDonald, M.D., Dallas, Texas

Magnolia Room A

Afternoon Session

Chairman: Stanley A. Brosman, M.D., Los Angeles

1:30—**Ultrasonic Treatment of Ureteral Calculi**—Roger B. Goodfriend, M.D., Los Gatos

2:15—**Dermatologic Problems in Urology**—Ronald M. Reisner, M.D., Los Angeles

3:00—**Intermission**

3:15—**Ureteroceles**—Donald B. Martin, M.D., Irvine

4:00—**Business meeting**

nake reservations now and plan to attend . . .

CMA PRESIDENTS' DINNER

Sunday evening, March 11
Disneyland Hotel, Anaheim

)inner will be at 7:30 p.m., immediately following the ·aditional Presidents' Reception at the CMA Annual ession, and the leaders of the CMA and the Woman's .uxiliary to the CMA will be honored. The dinner 'ill feature live music, entertainment, and awards and resentations formerly made during the House of Delegates sessions.

Tickets are $10.50 each. Tables seat 10 persons. For reservations, send check made out to WA-CMA to: Woman's Auxiliary to CMA, 10161 Broadview Place, Santa Ana 92705.

Chest Diseases

Important Notice: Advance registration *and* payment is required for the luncheon of the Section on Chest Diseases. Please return the reservation form with your payment ($7.50) if you expect to attend the luncheon and program.

RESERVATION FORM

Please reserve tickets for the luncheon program on Sunday, March 11, 1973 at $7.50 per ticket. Amount enclosed $.....

LUNCHEON with Speaker

Valvular Surgery—Albert Starr, M.D.
Professor of Surgery
Chief, Cardiopulmonary Surgery
University of Oregon Medical School
Portland, Oregon

Return This Application with Total Remittance to:
California Chapter
American College of Chest Physicians
424 Pendleton Way
Oakland, Ca 94621

Name _____

Address _____

City _____ State _____ Zip _____

Field of Practice _____

Make check payable to:
California Chapter, American College of Chest Physicians

Health of the School Age Child

RESERVATION FORM

Second Congress on Health of the School Age Child
March 10-11, 1973
Anaheim Convention Center

Registration Fee: $20.00, includes luncheons on Saturday, March 10, and Sunday, March 11

Checks are to be made payable to:
California Medical Association—Committee on School and College Health

Enclosed is my check or money order to cover enrollment in the Second Congress on Health of the School Age Child

Name _____

Address _____

City _____ State _____ Zip _____

Return This Form with Your Registration to:
Felix A. Schwarz,
Coordinator, CMA Committee on School and College Health
693 Sutter Street
San Francisco, Ca. 94102

Alcoholism and Other Drug Abuse

RESERVATION FORM

I wish to attend the Conference on Treatment for Alcoholism and Other Drug Abuse at the California Medical Association's Annual Scientific Assembly scheduled for Sunday, March 11, 1973 at the Disneyland Hotel.

Enclosed is my $10.00 check, payable to the CMA Committee on Alcoholism (includes cost of luncheon).

Name _____

Street Address _____

City _____ State _____ Zip _____

Mail to: Mrs. Gail Jara
California Medical Association
693 Sutter Street
San Francisco, Ca. 94102

Cardiopulmonary Medicine and Surgery

Important Notice: Advance registration AND payment is required for the Postgraduate Course on Cardiopulmonary Medicine and Surgery. Please return the accompanying reservation form with your payment ($25) if you expect to attend the postgraduate course. Luncheon is included in the registration fee.

RESERVATION FORM

Please enroll me in The Postgraduate Course on Cardiopulmonary Medicine and Surgery which will be held at the Disneyland Hotel, March 10, 1973.

REGISTRATION FEE: $25.

Tuition includes luncheon. Full tuition must accompany the application. Refunds will be made for cancellations made before March 2, 1973. Reservations will be closed March 5, 1973.

Please indicate if you will attend luncheon.
Yes _____ No _____

Return This Application with Total Remittance to:
CALIFORNIA CHAPTER
American College of Chest Physicians
424 Pendleton Way
Oakland, Ca. 94621

Name _____

Address _____

City _____ State _____ Zip _____

Field of Practice _____

Make check payable to:
California Chapter, American College of Chest Physicians

Scientific and Organizational Exhibits

Exhibit Hall, Disneyland Hotel

ACTION Peace Corps/VISTA—Ralph Coleman, San Diego. This exhibit is designed to introduce qualified health professionals to the programs of this voluntary agency of the U.S. Government—to create interest and, it is hoped, to obtain recruits.

The Adventure of Hospital Infection Control—Harvey A. Elder, M.D., Loma Linda University Medical Center, Loma Linda. Illustrates the role of post-operative wound infections. Related factors are shown, and an attempt is made to stimulate the observer to evaluate potential areas of improvement so that wound infection rates can be decreased.

American Association of Medical Assistants, State of California, Inc.—Thelma Colvin, San Diego. Brochures are available to acquaint physicians with the recognized medical assistants' organization—its goals and purposes. There will also be brochures for medical assistants on the National Certification Program.

Angiographic Evaluation of "Cold Hands"—Peggy Fritzche, M.D., Loma Linda University School of Medicine, Loma Linda. This exhibit will demonstrate the arteriographic pattern of a spectrum of vascular lesions responsible for vascular insufficiency to the upper extremity. The well-known pattern of atherosclerosis will be compared to that of Buerger's Disease, Polymyalgia arteritica, Takeyasu's Disease and Raynaud's Phenomena. Examples of upper extremity embolization will demonstrate etiologies such as fibrillation, myxoma, lupus erythematosus and thoracic outlet syndrome associated with thrombosis.

Birth Defect Centers—Dorothy H. Sutherland, National Foundation/March of Dimes, Orange County Chapter, Santa Ana. Description of the research, medical services and educational programs of the National Foundation/March of Dimes.

Bladder Catheter Care—Harvey A. Elder, M.D., Loma Linda University Medical Center, Loma Linda. Problems of catheter care, with illustrations of the mechanisms whereby bladder catheter care can lead to bacteriuria and a discussion of the complications that bacteriuria brings. A method of bladder catheterization that avoids many complications is presented with a review of the method as carried on at Loma Linda Medical Center. A teaching film on catheter care for nurses will be presented.

California Association of Medical Assistant Instructors—Virginia Frenger, Torrance. This exhibit features brochures, slides and course outlines concerning training programs for medical assistants and medical secretaries which are offered in California community colleges.

California Medical Association Certification and Accreditation of Continuing Medical Education Programs—Richard Manley, San Francisco. The Committee on Continuing Medical Education and CMA staff will answer questions, distribute certification reporting forms and assist physicians with forms. An electronic demonstration of the Continuing Medical Education Program's storage and retrieval system will be given. (Information on the CMA Accreditation of Continuing Medical Education Program for community hospitals and on the Consolidated Hospital Survey Program (JCAH-CMA) will also be available.) Your comments and suggestions for California's future role in continuing medical education will be welcomed.

California Medical Association Physician Placement Service—The coordinator of the Placement Service will be on hand throughout the meeting to discuss opportunities for practice in California, and to take listings for the Placement Bulletin.

CALIFORNIA MEDICINE—Journal of the California Medical Association. A display emphasizing the features of the Journal which have attracted most attention among CMA members and readers elsewhere throughout the world. Orders may be placed at the booth for gift subscriptions for medical students under the "Tomorrow's Physician" program. The booth will be staffed by the Managing Editor.

Common Dermatoses Seen in Office Practice—Harry Roth, M.D., Daly City. Presentation of the important diagnostic features of the common dermatoses, concentrating on three major entities—psoriasis, atopic dermatitis and contact dermatitis. The exhibit stresses the morphology of classical lesions, characteristic body distribution and key points in differential diagnosis. Illustrations of other skin lesions often confused with dermatoses are provided. Treatment with topical corticosteroids is briefly discussed in the context of two clinical double-blind trials of fluocinonide cream.

Electrocardiographic Monitoring via Telephone from Suburban Coronary Care Units—William S. Breall, M.D., San Francisco. Demonstration of electrocardiographic monitoring from 91 stations throughout the U.S., fed into a single receiving station in San Francisco, with a detailed illustration of a wide variety of abnormal electrocardographic arrhythmias and contours. Simulated coronary care setup with a live model, showing transmission from the model to the opposite side of the booth via telephone. Electrocardiographic transmission from the exhibit booth to the central station in San Francisco is available for any physician desiring an ECG transmission on himself.

Endometrial Biopsy in the Luteal Phase of the Cycle of Conception—William G. Karow, M.D., Southern California Fertility Institute, Los Angeles. Presentation of results and complications of 28 pregnancies in which endometrial biopsies were taken during the luteal phase of the conception cycle, selected from 1,000 consecutive biopsies taken from "infertility" patients as part of their evaluation. Summary of the outcome of 157 cases of endometrial biopsy in the luteal phase of conception, from the world literature of the

past 30 years, is presented for comparison. Enlarged microscopic transparencies are used to present the histological changes of the endometrium on each day of the luteal phase.

Feeding Techniques for the Cleft Palate Infant—Leslie M. Holve, M.D., Santa Monica. This exhibit presents an educational device for instruction of parents, students and allied health professionals in the special requirements for feeding a cleft palate child. Written and visual materials are used and various types of available equipment are demonstrated, with discussion of their advantages and disadvantages.

Ferromagnetic Silicone Vascular Occlusion: A Technique for Selective Tissue Infarction—Robert W. Rand, Ph.D., M.D., Department of Surgery and Neurosurgery, School of Medicine, University of California, Los Angeles. Illustration of technique for infarction of organs or tumors by injection of ferro-silicone material into selected arterial vessels under the control of a superconducting electromagnet. Liquid ferro-silicone is injected through angiographic catheters into a vessel feeding a target structure (e.g., tumor) and confined within the structure by a magnetic field until the material solidifies (vulcanizes). A demonstration of results of experimental and clinical applications of the technique is presented, as well as demonstrations of renal infarction for treatment of hypertension and splenic infarction for treatment of thrombocytopenia. Appropriate angiograms and histology are included.

Gonorrhea—Donald J. Pirozzi, M.D., Center for Disease Control, Atlanta. Gonorrhea is one of the most prevalent bacterial infections of adults in America. This exhibit emphasizes effective techniques for diagnosing the disease in males and females and the most recent treatment recommended by the Public Health Service. Use of Transgrow, a new medium for transport and growth of pathogenic *Neisseria*, is explained.

Hernia Repair without Disability—Irving L. Lichtenstein, M.D., Los Angeles. Anatomy of the inguinal area is redefined by means of artist's renditions, individually illuminated. Key elements of anesthesia and surgical repair are demonstrated, and the dynamics of wound healing are illustrated.

Life and Death Before Birth—Michael A. Fahey, M.D., Van Nuys. Prenatal development of the embryo and fetus is illustrated with specimens in all stages of development. Exclusive color photographs by Doctor A. W. Liley of New Zealand, considered by many to be the father of fetology, are presented, as well as color photographs dealing with changing standards of viability for high risk infants. Also included in the exhibit is a film on methods and results of abortion.

Lumbar Interbody Fusion: A Valuable Adjunct to Lumbar Disc Excision—Robert W. Rand, Ph.D., M.D., Department of Surgery and Neurosurgery, School of Medicine, University of California, Los Angeles. Presentation of the advantages of the addition of a lumbar posterior interbody fusion to standard lumbar disc excision procedures. Charts and literature will itemize the advantages of this procedure over disc excision alone and will suggest criteria for selection of patients. Some of the techniques for posterior interbody fusion will be briefly illustrated with schematic drawings.

Measurement of Cardiac Shunting in Cyanotic Children—Gary F. Gates, M.D., Memorial Hospital Medical Center of Long Beach. Intravenous injection of 99mTc-macroaggregated albumin followed by total body scanning with a gamma camera can quantitate right-to-left shunting in cyanotic children. The same examination also determines distribution of pulmonary blood flow between the lungs. Total body and lung scanning helps evaluate systemic and pulmonary blood flow changes following corrective cardiac surgery. Representative radionuclide studies are presented and compared to conventional cardiac catheterization results in the same patients. The examination has been performed on many children with cardiopulmonary disorders and appears to be safe, uncomplicated and accurate.

Management of Non-Narcotic Drug Dependency—Leon Marder, M.D., Drug Dependency Treatment Center, Rancho Los Amigos Hospital, Downey. This exhibit deals with a program of safe detoxification for barbiturate, sedative or minor tranquilizer drug-dependency. Treatment for the intoxicated state and "bad trip" reactions are also dealt with. Criteria for patient selection for the detoxification and rehabilitation programs are presented. The team treatment approach is shown in the audio-visual portion of the exhibit.

Modern Childbirth at Home—Joseph F. Griggs, M.D., The Claremont Foundation, Inc., Claremont. A silent motion picture with titles showing preparation for home childbirth, labor, delivery and post-partum examination and repair. The exhibit does not advocate or encourage home delivery, but seeks to show that, when not contraindicated, it can be carried out with reasonable ease and safety by incorporating modern methods.

The Neuroradiology of the "Chiasmal Syndrome"—Anton N. Hasso, M.D., Department of Radiology, School of Medicine, University of California, Los Angeles. Patients with the "chiasmal syndrome" form the basis of this study. Since pituitary adenomas with suprasellar extension may mimic purely extrasellar tumors whenever the sella turcica remains relatively intact, complete neuroradiological investigation is necessary to evaluate suspected sellar and/or parasellar masses. At the UCLA Medical Center pneumoencephalography with sectional tomography is employed to outline any mass and its contiguity with all surrounding intracranial structures. Selective angiography of the carotid vessels is a routine supplemental procedure used to define a mass which may be an aneurysm, show a tumor blush or cause vascular displacements. Visual field, neuroradiological findings and pathological diagnosis of various entities are presented with emphasis on the differential radiographic features.

"New" Gonorrhea: Stubborn or Resistant?—Morton Nelson, M.D., Alameda County Health Care Services Agency, Oakland. Based on the conclusion that gonorrhea can still be effectively treated by a single intramuscular injection of a sufficiently large dose of fast-acting penicillin, and that while penicillin has lost some of its once overwhelming effectiveness against *N. gonorrhea*, resistance has proved relative. Results with 225 patients at Alameda County Health Department VD Clinic in Oakland and a sequel study involving 332 male patients are presented.

Pacific Southwest Regional Medical Library Service—Betsey Beamish, Biomedical Library, University of California, Los Angeles. Demonstration of MEDLINE (MEDLARS On-Line), a new bibliographic searching capability now available to Pacific Southwest Regional Medical Library Service and selected health science institutions across the country. This exhibit provides an opportunity for physicians to observe the capabilities of the system and to become better users of both the new information retrieval techniques and the traditional library services. Also included is a health sciences core library collection consisting of basic books and journals most frequently used by physicians for patient care.

The Problem Drinker . . . and Driving: The Commutable Disease—Jordan Pollack, National Highway Traffic Safety Administration, Washington, D.C. Multi-media exhibit featuring

moving traffic "action" sequence and graphs, emphasizing that "Prevention Rx begins in your office."

Project Reentry—Mrs. James C. MacLaggan, California Medical Association Woman's Auxiliary. This exhibit deals with a training program for volunteers involved in resocialization of stroke victims.

Rehabilitation Services of the American Cancer Society—Marie Aylward, San Francisco. This exhibit depicts the rehabilitation visitor programs available to cancer patients throughout California. There is a graphic presentation of the questions related to the patient's physical, emotional and social adaptation to ostomy, mastectomy or laryngectomy surgery. American Cancer Society volunteer visitors representing each of the programs will be available to answer questions.

Rx Home Health Care: "Just What the Doctor Ordered"—Melvin Kirschner, M.D., California Association of Home Health Agencies, Pasadena. This exhibit will consist of photographs portraying the variety of services available to patients at home. A series of slides will illustrate aspects of patient care related to rehabilitation, teaching and supportive care. Information about home care will be provided by physicians and other health professionals.

Scientific Nutrition Education and Practice in Public Prenatal Clinics—Tom Brewer, M.D., Nutrition Action Group, San Francisco. This exhibit presents a display of visual aids used in teaching nutrition to prenatal patients, wall charts depicting data from several nutritional surveys and educational projects and a silent film entitled "Congenital Protein-Calorie Deficiency" made by Professor B. S. Platt of the Human Nutrition Institute, London School of Tropical Medicine.

Use of Dynamic Electrocardiography in Cardiac Diagnosis and Therapy—Harold L. Karpman, M.D., Beverly Hills. Demonstration of the clinical value of dynamic electrocardiography (Holter monitoring) in cardiac diagnosis and therapy. Major clinical uses of DCG in diagnosis and therapy are illustrated by actual case reports for 10 different diagnostic applications and four therapeutic evaluations are presented. Emphasis on detection of abnormalities which may presage sudden death and the objective diagnosis of angina.

Two Years Experience with a New Ventricular Tracking Standby Pacemaker and Data Transmission Follow-up System—Albert Starr, M.D., School of Medicine, University of Oregon, Portland. The purpose of this exhibit is to outline the features of a new ventricular tracking standby pacemaker. This implantable pacemaker provides a nonstimulating marker pulse or a stimulating pulse depending upon the patient's own rate. The marker pulse can be used in a data transmission system in order to determine the function of the sensing mechanism while the stimulating pulse provides information concerning battery depletion. Over 150 clinical implants and two years of patient follow-up using the data transmission system are reviewed.

The following exhibits, of special interest to those attending the Second Congress on Health of the School Age Child, March 10-11, 1973, will be on display outside Santa Ana Rooms 1 and 2 in the Anaheim Convention Center during the Congress:

California Association for Neurologically Handicapped Children John Seymour, Garden Grove.

California Dental Association/Southern California Dental Association Joint Committee on Dental Health Education—George Holiday, Los Angeles.

National Alliance Concerned with School-Age Parents—Georgiana Selstad, Agoura.

San Luis Medical Clinic—Patricia C. Lindamood, San Luis Obispo.

Visit Technical Exhibits

In the Exhibit Hall
Disneyland Convention Complex

March 10-14, 1973

9:00 a.m. to 5:00 p.m.

WOMAN'S AUXILIARY

FORTY-THIRD ANNUAL CONVENTION

MARCH 10-13, 1973

Headquarters: Disneyland Hotel, Anaheim

Convention Chairman: Mrs. David O. MacLachlan
Convention Co-Chairman: Mrs. Warren L. Bostick

REGISTRATION: New Ballroom Foyer

Saturday, March 10—noon to 4:00 p.m.
Sunday, March 11—10:30 a.m. to 5:00 p.m.
Monday, March 12—8:00 a.m. to noon
Tuesday, March 13—8:00 a.m. to 10:00 a.m.

SATURDAY, March 10—Pre-Convention

1:00 p.m.—Presentation of Mrs. Ward L. Hart, Auxiliary President, to CMA House of Delegates, South and Center Ballrooms.

4:00 p.m.—Executive Committee Meeting, President's Suite

SUNDAY, March 11

1:00 p.m.—Pre-Convention Board Meeting, Pacific Room, Sierra Tower

6:30 p.m.—Presidents' Reception, New Ballroom Complex

7:30 p.m.—Presidents' Dinner, New Ballroom Complex

MONDAY, March 12

8:30 a.m.—Opening Session of House of Delegates, New Ballroom Complex, South and Center Ballrooms

11:30 a.m.—President's Luncheon, North Ballroom

1:30 p.m.—Afternoon Session of House of Delegates, South and Center Ballrooms

5:00 p.m.—Champagne Tour and Dinner on the Queen Mary

TUESDAY, March 13

8:30 a.m.—Final Session of House of Delegates, South and Center Ballrooms

1:00 p.m.—Orientation Meeting, Pacific Room, Sierra Tower

1:30 p.m.—Presentation of Mrs. Thomas A. Gibson, Incoming Auxiliary President, to the CMA House of Delegates, South and Center Ballrooms

4:00 p.m.—Post-Convention Board Meeting, Pacific Room, Sierra Tower

HOSPITALITY CENTER—Cerritos Room, Sierra Tower

Sunday, March 11—9:00 a.m. to 4:00 p.m.
Monday, March 12—8:00 a.m. to 11:30 a.m.
Tuesday, March 13—8:00 a.m. to 11:30 a.m.



MRS. WARD L. HART
President



MRS. THOMAS A. GIBSON
President-Elect

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Thomas Elmendorf, Willows.....*President-Elect*
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Henry V. Eastman, Tustin...*Vice-Speaker, House of Delegates*
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Roberta F. Fenlon, San Francisco....*Immediate Past President*
Helen B. Weyrauch, San Francisco.....*Secretary*
Malcolm S. M. Watts, San Francisco.....*Editor*
Robert L. Thomas.....*Executive Director*
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House of Delegates

TOTAL DELEGATES (367)

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John T. Saidy, San Mateo.....Chairman of the Council
E. Kash Rose, Napa.....Vice-Chairman of the Council
Roberta F. Fenlon, San Francisco.....Immediate Past President
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Malcolm S. M. Watts, San Francisco.....Editor

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Orrin S. Cook (1975).....Eleventh District
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C. John Tupper (1973).....Scientific Board Representative

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(Not available at press time)	
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FORTY FIRST (2)	
Grunigen, Forest J.	
FRESNO (6)	
Barman, Martin L.	Chandler, Hubert
Millar, Max	Packer, Benjamin
Smith, Robb	Moore, Ronald
Smith, Troy	Rosenstein, Morton
Spaulding, Robert	Tostenson, N. E.
Steinberg, Theodore	Wilde, N. John
HUMBOLDT-DEL NORTE (2)	
(Not available at press time)	
IMPERIAL (2)	
(Not available at press time)	
INYO-MONO (2)	
(Not available at press time)	
KERN (4)	
Ardell, David S.	Anderson, Joseph E., Jr.
Benedict, J. Frank	Faulstick, Dyrel A.
Reese, Thomas V.	Hagen, William A.
Spaulding, Keith W.	Siemon, Glenn
KINGS (2)	
Brookshier, R. W.	Lusby, Richard A.
Kerr, E. E.	Monfore, Thomas E.
LASSEN-PLUMAS-MODOC-SIERRA (2)	
Christenson, Steven	Bross, Willard S., Jr.
Korver, Kenneth G.	Daehler, David G.
LOS ANGELES (90)	
Adams, Donald A.	Adler, Denis C.
Alter, Marvin S.	Affley, Harry J.

Delegates	*Alternates*
LOS ANGELES (Continued)	
Amerongen, Frederick K.	Alban, Seymour L.
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Briney, Allan K.	Chusid, Lawrence A.
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Carney, Padraig	Critchlow, Francis B.
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D'Orazio, Edward	Dodge, David R., Jr.
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Dukes, Robert W.	Edwardh, Orville H.
Ellerbeck, Walter E.	Elconin, Kenneth B.
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Fritz, Samuel H.	Grobert, Marshall J.
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Greco, Donald J.	Guiss, Lewis W.
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Haskell, M. M.	Harwell, Julian L.
Hassen, Mitchell	Heister, Saul
Hill, Harry E.	Holtz, Marvin J.
Hoffman, Peter L.	Hoyos, Jorge
Horner, David B.	Hyman, William
Kaminski, Kenneth L.	Japenga, Jack W.
Kaspar, Friedrich H.	Jenkins, Charles E.
Kaufman, Gene B.	Jones, Henry A.
Kaufmann, Bertram J., Jr.	Karlan, Mitchell S.
Keltner, Mark R.	Karns, Robert M.
Ketcham, Burton E.	Katz, Edward E.
Killeen, Raymond N. F.	Kelley, Walter W.
Klein, E. Philip	Kolpack, Marvin W.
Kohler, Hugh F.	Kuhn, Robert
Kugel, Arthur I.	Landon, Charles W.
Lopez, Charles J.	Lusk, Harry A.
McCaffery, James M.	Martini, M. Michael
Mailman, Richard H.	Massey, Ben D., Jr.
May, Lewis H. V.	Mazurek, Richard J.
Meine, Emile L., Jr.	McElwee, Charles B.
Miller, Richard D.	Michels, Arthur G.
Milliken, Ralph M.	Mizener, Wilson
Morrieta, A. J., Jr.	Murphy, Terrence J.
Neuenschwander, Robert S.	Nishizawa, Akira
Newhouse, Robert M.	Odou, Eugene R.
Olch, David	Okie, Theodore B.
Ottalini, Guy A.	Pallette, Edward M.
Penka, Ernest J.	Palmer, Jay J.
Penn, Sidney	Rago, Marco R.
Pettit, Richard D.	Rayman, Irving B.
Pollack, John V.	Redewill, Francis H., Jr.
Richards, Melvin	Robert, James C., Jr.
Rockney, Robert E.	Rowell, Homer A.
Rubell, Earl B.	Sanchez, Alphonso R.
Rudy, Norman E.	Schmit, Robert A.
Sakaguchi, Sanbo S.	Seidman, Donald R.
Shearer, S. K.	Sewak, John H.
Smith, Thayer A.	Slater, Roger A.
Stauffer, Floyd R.	Steen, Alan M.
Sullivant, Richard A.	Sue, Julius F.
Todt, Jack C.	Titus, Edward D.
Trumbull, William E.	Todd, William H.
Wandling, Harold S.	Trimble, David N.
Watson, Robert L., Jr.	Valvo, Carlton F.
Weil, William S.	van Adelsberg, Stephan B.
Weiss, Benjamin J.	Westerbeck, Charles
Wiater, Edward J.	White, John R.
Williams, Henry S.	Wigton, John R.
Wong, Thomas A.	Wong, Alton S. K.
Wright, Carter R., Jr.	Zager, Albert
Wunderlich, Edwin	Zinn, Williard J.
Zinn, Alexander N.	Vacancy
MARIN (4)	
Costanza, David	Belknap, Marjorie
Lee, John	Franzblau, Michael
Tavel, Frank	Lesko, Clarence
White, A. H.	Weden, Elmer, Jr.
MENDOCINO-LAKE (2)	
(Not available at press time)	
MERCED-MARIPOSA (2)	
Anglin, John V.	Patterson, Kalfus W.
Faber, Dorian R.	Rugani, Peter R.
MONTEREY (3)	
Eldredge, Eugene E.	Baldwin, John N.
Klinefelter, Robert P.	Elliott, Thomas S.
Turner, Joseph E.	Taugher, Donald F.
NAPA (2)	
Brignoli, Walter H.	Ehrlich, Harry
Hemphill, Arthur C.	Queary, Charles H.
ORANGE (15)	
Altman, Richard	Bostick, Warren L.
Andrews, Alan V.	Burrill, C. William
Ball, Dexter T.	Dorsey, Thomas
Bouchelle, McLemore	Doyle, James R.
Carroll, Vincent	Farrer, John F.
Donaldson, A. Norton	Gavin, Martin J.
Geddes, David	Helton, Robert
Gerrie, Wallace	Llewellyn, Gene
Higger, Harvey L.	Nadridge, Maurice
Kay, Fred M.	Opfell, Harriet
McFarland, Philip H.	Robinson, Tom W.
Mosier, Laurance A.	Singer, Melville I.
Plows, Charles W.	Stafford, William
Stonestreet, Marshall	Stock, Leo
Thompson, Arthur	Wightman, Ardath
PLACER-NEVADA (2)	
(Not available at press time)	
RIVERSIDE (5)	
Haller, Stefan K.	Lansing, J. Dee
Pitchford, Clyde A.	Rafferty, Robert
Silver, Harrison E.	Duino, Mikel
Stone, Herman H.	Reeves, Nile I.
Zweig, Robert M.	Vacancy
SACRAMENTO (9)	
Babich, John M.	Affleck, James
Bramham, James	Bittner, William
Demorest, Byron	Bonser, Quentin
Fong, William	Bliss, Howard
Brown, Frank	Loyd, Herlan
Go, Henry	Martin, James
Gross, George	O'Kane, Calvin
Janushkowsky, Alex	Pope, Glenn
Reilly, Philip	Schubert, James
SAN BENITO (2)	
Badke, Robert T.	Haruff, John J.
Brooks, Fisk	Kirch, Joseph L.
SAN BERNARDINO (7)	
Harer, W. Benson, Jr.	Allen, Byron
Hendrickson, Merlin	Ballard, Ross L.
Miano, Ben D. A.	Carmack, Charles
Mortensen, John	Gillespie, James
Sprague, C. P.	Kirshbaum, Robert
Sterling, Allen	McAllister, John
Wake, Donald	Moseley, Wendell
SAN DIEGO (16)	
Bethard, William F.	Adams, William T.
Flaiz, John W.	Bishop, John A.
Freeman, Gordon R.	Depew, Harry W.
Hall, Winston C.	Frye, Frederick A.
Hippen, Robert L.	Gleason, Matthew C.
Herrick, W. C.	Heard, Jerome L.
Kirtland, Howard B.	Hindman, Robert E.
Lococo, Thomas N.	Maas, Harry E.
Mitchell, W. Byron	Minor, Winston
Peabody, Homer D., Jr.	Randel, Harvey O.
Peck, J. Haddon A., Jr.	Shaw, Walter M.
Peck, Sam	Trombold, John S.
Pierangelo, Anthony J.	Weiss, Harry A.
Plumb, Robert T.	Wilson, Earl L.
Smith, Sam	Vacancy
Vacancy	Vacancy
SAN FRANCISCO (20)	
Baer, Charlotte C.	Allen, David W.
Barrios, Xavier O.	Coleman, Arthur H.
Bender, William T.	Cook, Robert E.
Biskind, Gerson R.	Dulay, Fernando V.
Cohn, Bradford	Franzi, Antonio J.
Foster, Sidney E.	Gibbons, Henry III
Herzog, George K., Jr.	Gorney, Mark
Lee, Jane F.	Gross, Sheldon
Levin, Sheldon	Heer, F. William
Lindner, Harold H.	Kelley, Edward T.
Palmer, Richard J.	King, Charles D.
Pevehouse, Byron C.	Lee, Harry
Pillsbury, Philip L.	Molyneaux, Glenn M.
Rixford, Emmet L.	Oscherwitz, Mark
Robinson, Saul J.	Paver, Robert L.
Saunders, John B. deC.M.	Sachs, David D.
Schaffarzick, Ralph W.	Salomon, Maurice S.
Scholten, Paul	Sherman, Robert S., Jr.
Solari, Rafael A.	Weinreb, Irwin
Wayburn, Edgar	White, Laurens

Delegates	*Alternates*

SAN JOAQUIN (4)

(Not available at press time)

SAN LUIS OBISPO (2)

Chambers, James R.	Hughell, J. Edward
Cletsoway, Richard W.	Osibin, Willard S.

SAN MATEO (8)

Geraci, Charles L.	Beames, Ranulf P.
Hart, Ward L.	Bell, Leo S.
Healy, Francis A.	Feinstein, Myron S.
Hills, Oscar W.	Hansen, James R.
Kohn, Martin M.	Johnson, Harold P., Jr.
Lindsey, Howard W.	Marquette, Richard H.
Richanbach, Henry S.	Packard, Peter
Rossiter, Stanford B.	Richards, Marvin D.

SANTA BARBARA (5)

Blanchard, John P.	Elam, Eldon
Dahlen, Gregory A.	Feldsted, E. T.
McNiece, Kenneth J.	Holderman, Henry L.
Rutten, R. John	Kucera, William J.
Ziemba, Joseph	Williams, Robert G.

SANTA CLARA (15)

Armstrong, Frederick	Austin, Glenn
Boice, Clyde L.	Bright, Ross
Burnett, Robert D.	Elliott, Hugh
Drinker, Henry R., Jr.	Kornfield, Harrison
Fox, Leon P.	McCort, James J.
Giansiracusa, Frank	Nola, Vincent
Grossman, Maurice	Pillsbury, R. Cree
Kaufman, S. Fred	Reeves, William
Lee, R. Hewlett	Rodenbaugh, F. Hase
Liston, Edward	(Name not available)
Neubauer, Ivan	Truitt, Robert
O'Neill, Robert J.	Walworth, David
Rowles, Donald	Whelan, Harry G.
Scarborough, C. Gerald	Williams J. Hicks
(Name not available)	Zlotnick, David

SANTA CRUZ (3)

Jones, Robert C.	Dunn, Bruce L.
King, John W.	Eicholz, John L.
Nelson, Carl	Liddicoat, Douglas A.

SHASTA-TRINITY (2)

(Not available at press time)

SISKIYOU (2)

Christy, John R.	Klatt, Lloyd I.
Howe, Roger	Lund, Johanna E.

SOLANO (2)

Gullock, Alvin H.	Miller, John C.
Lonsdale, Howard C.	Vincent, Keith E.

SONOMA (3)

Anderson, Raymond C.	Archambeau, Paul L.
Lones, Frank E.	Born, Freeman W.
Olney, John M.	VanGiesen, Donald R.

Delegates	*Alternates*

STANISLAUS (3)

(Not available at press time)

TEHAMA (2)

Gumm, Melvin	Jourdan, H. W.
Ingle, G. W.	Wood, O. T.

TULARE (3)

Geiger, E. Robert	Markoff, Sven C.
Goettle, James W.	Mekemson, Robert R.
Natzke, Richard	Wahlen, Donald E.

VENTURA (4)

(Not available at press time)

YOLO (2)

Wisner, F. Hal	van Muyden, Wim
Young, Corbin	Vaughn, T. Neil

YUBA-SUTTER-COLUSA (2)

Heckman, John R.	Toller, Jerry F.
Walkin, Fletcher L.	Wallace, Robert N.

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Dutra, Frank R.	Gross, George A.
Einstein, Hans E.	Halter, Bert L.
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Hockwald, Robert S.	Martin, James W.
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Monsen, David C. G.	Vandervoort, Herbert E.
Opfell, Richard	
Palmer, John M.	
Richards, Victor	
Stein, Justin J.	
Tupper, C. John	

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Schaupp, Karl L., Sr.....1943	Bostick, Warren L.....1961
Cline, John W.....1947	Wheeler, Omer W.....1962
Askey, E. Vincent.....1948	Sherman, Samuel R.....1963
Cass, Donald 1950	Doyle, James C.....1964
MacLean, H. Gordon.....1951	Teall, Ralph C.....1965
Green, John W.....1953	MacLaggan, James C.....1966
Morrison, Arlo A.....1954	Morrison, John G.....1967
Shipman, Sidney J.....1955	Todd, Malcolm C.....1968
MacDonald, Frank A.....1957	Miller, Albert G.....1969
West, Francis E.....1958	Burnett, Ralph W.....1970
Reynolds, T. Eric.....1959	Fenlon, Roberta F.....1971

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Wilbur, Dwight L.

House of Delegates • 1973 Annual Session

AGENDA

New Ballroom, Disneyland Hotel Convention Complex

Speaker.....Joseph F. Boyle, Los Angeles
Vice-Speaker.....Henry V. Eastman, Tustin
Secretary.....Helen B. Weyrauch, San Francisco

FIRST MEETING, Saturday, March 10, 1973
REGISTRATION—12:00 Noon
MEETING STARTS—1:00 p.m. Sharp

1. Call to order. (Invocation and Pledge of Allegiance)
2. Announcement of Reference Committees:
 - Committee on Credentials.
 - Reference Committee A—Community and Environmental Health
 - Reference Committee B-1—Government Medical Programs
 - Reference Committee B-2—Government Medical Programs
 - Reference Committee C-1—Medical Economics, Insurance & Prepayment
 - Reference Committee C-2—Medical Economics, Insurance & Prepayment
 - Reference Committee D-1—Scientific & Educational Activities
 - Reference Committee D-2—Scientific & Educational Activities
 - Reference Committee E-1—Professional & Public Relations
 - Reference Committee E-2—Professional & Public Relations
 - Reference Committee F—Finance
 - Reference Committee G—Constitution & Bylaws
 - Reference Committee H—California Blue Shield

2a. Miscellaneous Announcements.
3. Honored Guests.
4. Report of the Committee on Credentials, and Organization of the House of Delegates—Roll Call.
5. Recognition of President of Woman's Auxiliary to the CMA—Mrs. Ward L. Hart.
6. Address by President—Jean F. Crum.
7. Report of the President—Jean F. Crum.
8. Report of the President-Elect—Thomas Elmendorf.
9. Report of the Speaker and Vice-Speaker of the House of Delegates—Joseph F. Boyle and Henry V. Eastman.
10. Report of the Trustees of the California Medical Association—Jean F. Crum.
11. Report of the Physicians' Benevolence Fund, Inc.—Jean F. Crum.
12. Report of the Secretary—Helen B. Weyrauch.
13. Report of the Editor—Malcolm S. M. Watts.
14. Report of the Executive Director—Robert L. Thomas.
15. Report of Legal Counsel—Hassard, Bonnington, Rogers & Huber.
16. Report of the Executive Committee—Jean F. Crum.
17. Report of the Council—John T. Saidy, Chairman.
18. Report of California Blue Shield Trustees—Marvin J. Shapiro, Chairman.
19. Reports of Commissions.
20. Reports of other Committees.
21. Old and unfinished business.
22. New business.
23. Adjournment.

SECOND MEETING, Tuesday, March 13, 1973
REGISTRATION—12:00 Noon
MEETING STARTS—1:30 p.m.
(To be recessed and reconvened at 9:00 a.m. Wednesday, March 14)

1. Call to order.
2. Supplemental report of Credentials Committee—Roll Call.
3. Address by President-Elect—Thomas Elmendorf.
4. Introduction of President-Elect of Woman's Auxiliary—Mrs. Thomas A. Gibson.
5. Secretary's Announcement of Council's selection of time and place for the 1974 Annual Session.
6. Election of Officers.
7. Report of Reference Committee G. (Constitution and Bylaws)
8. Election of Delegates and Alternates to the American Medical Association.
9. Election of California Blue Shield Trustees.
10. Reports of Reference Committees.
11. Unfinished business.
12. New business.
13. Presentation of Officers
14. Adjournment

Proposed CMA Constitutional Amendments

FOR ACTION IN 1973

Six Constitutional amendments were introduced in the 1972 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before they come before the House of Delegates for action.

ARTICLE II, SECTION 1—CLASSES OF MEMBERS

Constitutional Amendment 1-72 Committee G

Introduced by: Paul Scholten, M.D.

WHEREAS, "free choice" is a prime tenet of the medical profession; and

WHEREAS, "required membership" is directly contrary to this prime tenet; and

WHEREAS, the recent poll conducted by the CMA as well as referendums by component medical societies indicated the desire of a substantial group of physicians to exercise their "free choice"; now, therefore, be it

Resolved: That the Constitution of the CMA be amended to include the classification of Independent Member. Such member would pay full dues to his component medical society and receive full benefits therefrom; such member *may* join the CMA by paying full dues, from which he would receive full benefits; and, be it further

Resolved: That Article II, Section 1, be amended by adding the word in italics: "The members of this Association shall consist of Active, Associate, *Independent,* Honorary, Retired, Life and Affiliate members."

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

ARTICLE I, SECTION 3—VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

Constitutional Amendment 2-72 Committee G

Introduced by: James W. Goettle, M.D.
Representing: Tulare County Medical Society

WHEREAS, the present bylaws of the CMA make membership in the AMA and CMA compulsory to all members of a component county medical society; and

WHEREAS, the medical profession has always vigorously defended the concept of "freedom of choice" in health care, but will not give this freedom of choice to its members as numerous other states now do; and

WHEREAS, freedom of choice has always been beneficial to professional people in the long run, for it makes the leaders of such organizations more responsive to members' desires as the history of our country has so demonstrated to the world; now, therefore, be it

Resolved: That the CMA Constitution be amended to read as follows: (Article I, Section 3) members of local county medical societies in the State of California have the freedom to decide individually whether they wish to join the CMA or AMA, singly or in combination.

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

ARTICLE I, SECTION 3—PROPOSED CALIFORNIA MEDICAL ASSOCIATION CONSTITUTIONAL AMENDMENT PERMITTING VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

Constitutional Amendment 3-72 Committee G

Introduced by: Allan K. Briney, M.D.
Representing: Los Angeles County

WHEREAS, the present Bylaws of the California Medical Association make membership in the California Medical Association and the American Medical Association compulsory to all members of a component county medical society; and

WHEREAS, we, as a profession, vigorously defend the principle of "freedom of choice" in health care, yet deny individual members of county medical societies the freedom of deciding whether or not they wish to belong to the California Medical Association or American Medical Association; and

WHEREAS, each physician is quite capable of deciding whether there are sufficient advantages or insufficient advantages to maintaining membership in all three organizations; and

WHEREAS, mandatory membership in one organization (CMA and AMA) in order to maintain membership in another (local medical society) significantly interferes with the privilege of setting priorities as to organizational commitments, such as belonging to specialty societies; and

WHEREAS, in forty states a local county medi-

cal association member may decide for himself whether he also wishes to maintain membership in the state and national medical associations; e.g., New York and Massachusetts; and

WHEREAS, professional liability insurance carriers have no requirements about California Medical Association or American Medical Association membership for coverage of a county medical society member; and

WHEREAS, in a free and democratic society it would seem reasonable and consistent that membership in all medical societies should be voluntary, with each society attracting members on its own merits; and

WHEREAS, when a local county medical association collects dues for a state and national medical association, the individual dues-payer tends to lump all these dues together as "county medical society dues", feeling he may not be "getting his money's worth"; and

WHEREAS, there is widespread feeling among local county medical association members that the CMA and AMA have long ago lost their "grass roots" contact and cannot speak authoritatively for the medical profession; and

WHEREAS, recent polls of the Los Angeles, Orange, San Diego and San Francisco County Medical Associations have overwhelmingly favored voluntary membership by an average of four to one, as opposed to compulsory membership; and

WHEREAS, a national poll by *Medical Opinion* magazine, published in November, 1971, showed 82% favoring voluntary membership in the American Medical Association; and

WHEREAS, results of the recent CMA opinion poll are inconclusive and misleading, due to substitution of the words *involuntary* and *compulsory* specified in Bylaws Amendment 22-71 authorizing the poll, by the words *separate* and *unified;* now, therefore, be it

Resolved: That Article I, Section 3, be amended as follows:

> This Association is an organization composed of the component societies and their members who are members of this Association, the House of Delegates, the Council, the Scientific Board, the Scientific Assembly, Bureaus, Commissions and Standing Committees.

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

* * *

ARTICLE III, PART A, SECTION 1(d)—VOTING PRIVILEGES FOR SCIENTIFIC BOARD REPRESENTATIVES IN THE HOUSE OF DELEGATES

Constitutional Amendment 4-72 Committee G

Introduced by: Council

Resolved: That Article III, Part A, Section 1 (d)—House of Delegates composition shall be amended by deleting the words in brackets and adding the words in italics, so that this Subsection shall now read:

"(d) Ex officio, [without] *with* the right to vote, [eighteen (18)] *twenty-one (21)* members of the Scientific Board selected as provided in the Bylaws; and . . ."

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

* * *

DELEGATES AND ALTERNATES TO AMA SHALL BE EX OFFICIO DELEGATES OF CMA

Constitutional Amendment 5-72 Committee G

Introduced by: Lawrence E. Reck, M.D.
Representing: 1st District

Resolved: That Article III, Part A, Section 1, be amended by adding a new sub-section (f) which reads as follows:

(f) *Ex officio, without the right to vote, the officers, the delegates and alternate delegates to the American Medical Association, who are not otherwise members of the House of Delegates of this Association.*

ACTION: Adopted above substitute Constitutional Amendment No. 5-72 as substitute for Resolution No. 62-72. Tabled for one year. To be acted upon at the 1973 House of Delegates.

* * *

ARTICLE III—GOVERNMENT OF THE ASSOCIATION
PART A—HOUSE OF DELEGATES—COMPOSITION
SECTIONS 1, 2, 4

Constitutional Amendment 6-72 Committee G

Introduced by: E. Kash Rose, M.D.

Resolved: That Article III, Part A, Section 1, be amended by adding a new sub-section (g) which reads as follows: *(g) Delegates elected by duly enrolled medical students in good standing at accredited schools of medicine in California;* and, be it further

Resolved: That Article III, Part A, Section 2, be amended by adding the words in italics, to read as follows:

> *As the Bylaws shall further provide, the duly enrolled medical students in good standing at each accredited school of medicine located in California shall be entitled to elect one delegate from each such school;* and, be it further

Resolved: That Article III, Part A, Section 4, be amended by adding the words in italics, to read as follows:

> *Delegates and alternates elected from each school of medicine shall serve for a term of one year.*

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

Reports of officers, commissions and committees of the California Medical Association, together with the following audited financial statements for the fiscal year ended June 30, 1972, are printed in the Annual Report Bulletin, which is distributed to Delegates and Alternates before the meeting of the House of Delegates. The Bulletin is also available to any member of the Association on request directed to Robert L. Thomas, Executive Director, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

FINANCIAL REPORTS

CALIFORNIA MEDICAL ASSOCIATION AND TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

(See pages 40 to 44)

REPORT OF
Certified Public Accountants

CALIFORNIA MEDICAL ASSOCIATION:

We have examined the balance sheets of California Medical Association and Trustees of the California Medical Association at June 30, 1972, and the related statements of income and expenses and statement of excess of assets over liabilities for the year then ended. Our examinations were made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the statements referred to above present fairly the financial positions of California Medical Association and Trustees of the California Medical Association at June 30, 1972, and the results of their operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year.

JOHN F. FORBES & COMPANY

San Francisco, California
August 18, 1972

CALIFORNIA MEDICAL ASSOCIATION
(A Nonprofit Association)

Balance Sheet, June 30, 1972 and 1971, and Comparison

	JUNE 30 1972	JUNE 30 1971	Increase (Decrease)
ASSETS			
CASH:			
Commercial accounts	$ 20,777	$ 21,559	$ *(782)*
Savings account	657,280	96,469	560,811
Total cash	678,057	118,028	560,029
CERTIFICATES OF DEPOSIT—MATURED JULY 27, 1972	750,000	1,250,000	*(500,000)*
ACCOUNTS RECEIVABLE, NET	108,510	116,993	*(8,483)*
ACCRUED INTEREST	6,000	8,586	*(2,586)*
NOTES RECEIVABLE:			
Central California Blood Bank	46,418	56,287	*(9,869)*
Other	800	1,600	*(800)*
Total notes receivable	47,218	57,887	*(10,669)*
PREPAID EXPENSES AND OTHER ASSETS:			
Retirement program premium (Note 1)	29,267	24,434	4,833
Insurance	4,575	5,102	*(527)*
Deposits	7,777	4,346	3,431
Other	10,706	8,599	2,107
Total prepaid expenses and other assets	52,325	42,481	9,844
OFFICE FURNITURE AND EQUIPMENT (Notes 2 and 3)	161,388	37,807	123,581
NOTE AND ACCOUNTS RECEIVABLE, AFFILIATED ORGANIZATIONS:			
Trustees of the California Medical Association:			
Demand note with interest at 4% per year	125,000	125,000	
Account receivable	35,072	16,138	18,934
	160,072	141,138	18,934
Other—Accounts receivable:			
Six Ninety Three Sutter Publications, Inc.	4,291	23,730	(19,439)
California Medical Education and Research Foundation, Inc.	2,565	1,157	1,408
Miscellaneous	9,516	2,187	7,329
Total note and accounts receivable, affiliated organizations	176,444	168,212	8,232
	$1,979,942	$1,799,994	$179,948
LIABILITIES			
ACCOUNTS PAYABLE:			
American Medical Association	$ 48,857	$ 49,270	$ *(413)*
Other	36,779	39,421	*(2,642)*
Total accounts payable	85,636	88,691	*(3,055)*
DUE TO AFFILIATED ORGANIZATION—PHYSICIANS' BENEVOLENCE FUND, INC.	24,872	23,775	1,097
LONG-TERM DEBT—EQUIPMENT LEASE CONTRACT (Note 3)	121,445		121,445
DEFERRED INCOME—DUES AND SUBSCRIPTIONS APPLICABLE TO THE SUCCEEDING FISCAL YEAR	1,258,939	1,264,588	*(5,649)*
Total liabilities	1,490,892	1,377,054	113,838
EXCESS OF ASSETS OVER LIABILITIES (Note 4)	489,050	422,940	66,110
	$1,979,942	$1,799,994	$179,948

See notes to financial statements.

Statement of Excess of Assets Over Liabilities Years Ended June 30, 1972 and 1971, and Comparison

	YEAR ENDED JUNE 30		
	1972	1971	Increase
UNRESTRICTED:			
Balance, beginning of year	$ 257,875	$ 254,450	$ 3,425
Excess of income over expenses for the year	66,110	6,849	59,261
Transfer to restricted	33,055	3,424	29,630
	33,055	3,425	29,631
Balance, end of year	290,930	257,875	33,055
RESTRICATED AS TO USE (Note 4):			
Balance, beginning of year	165,065	161,641	3,424
Transfer from unrestricted	33,055	3,424	29,631
Balance, end of year	198,120	165,065	33,055
EXCESS OF ASSETS OVER LIABILITIES	$ 489,050	$ 422,940	$ 66,110

See notes to financial statements.

Statement of Income and Expenses Years Ended June 30, 1972 and 1971, and Comparison

	YEAR ENDED JUNE 30		
	1972	1971	Increase (Decrease)
INCOME:			
Membership dues, less portion allocated to subscriptions to "California Medicine"	$2,424,523	$2,169,690	$254,833
Less collection fee allowed county societies	22,014		22,014
Net membership dues	2,402,509	2,169,690	232,819
Booth rentals at annual session	41,989	42,535	*(546)*
Fees, postgraduate courses	20,310	15,090	5,220
Fee for collection of American Medical Association dues	25,375	25,834	*(459)*
Interest earned	62,591	54,370	8,221
Other	105	64	41
Total income	2,552,879	2,307,583	245,296
EXPENSES:			
Physicians' Services and Programs	369,774	338,035	31,739
Divisional Programs	1,688,782	1,518,402	170,380
General expenses	387,855	374,013	13,842
	2,446,411	2,230,450	215,961
Contributions	37,312	49,208	*(11,896)*
Excess of expenses over income "California Medicine"	24,504	21,076	3,428
Total	2,508,227	2,300,734	207,493
EXCESS OF INCOME OVER EXPENSES BEFORE NET INCOME OF TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION	44,652	6,849	37,803
NET INCOME OF TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION	21,458		21,458
EXCESS OF INCOME OVER EXPENSES	$ 66,110	$ 6,849	$ 59,261

See notes to financial statements.

CALIFORNIA MEDICAL ASSOCIATION
(A Nonprofit Corporation)

Notes to Financial Statements

NOTE:

1. RETIREMENT PROGRAM

In addition to the Group Pension Program which became effective on January 1, 1961, the California Medical Association has arranged for the funding of a Past Service Pension Plan for certain full-time employees. This resulted in an additional liability of $62,734 which is being amortized over 20 years from January 1, 1966. The Travelers' Insurance Company has underwritten the plan and will furnish annuity contracts as eligible employees retire. Because the current service benefits and all of the benefits for retired employees have already been purchased under the contract, there is a liability only for the unfunded value of vested benefits. This liability amounted to $37,770 on January 1, 1972. It is neither recorded on the books of the Association nor included in the accompanying balance sheet.

The pension expense for the year was $50,613. This expense is determined by the underwriter each year, and may vary, depending on new qualifying employees, and credits arising from qualifying employees leaving the Association.

2. OFFICE FURNITURE AND EQUIPMENT

Acquisitions prior to July 1, 1966 are carried at a nominal amount of $1. At May 13, 1966, a firm of appraisers estimated that the sound value of assets then owned was $104,415. Assets acquired after July 1, 1966, are summarized as follows:

	Cost		Depreciation or Amortization
Office furniture and equipment: Balance, July 1, 1971	$ 77,669		$39,862
Purchased during the current year (see Note 3)	138,200		
Provision for the current year			14,387
Sales and trade-ins	*(269)*		*(37)*
Balance, June 30, 1972	$215,600		$54,212
Net book value		$161,388	

Depreciation is based on the estimated useful lives of the property (5 to 10 years) and the straight line method.

3. LONG-TERM DEBT

Certain equipment for which the Association has entered into a lease is accounted for as purchased equipment. The cost of this equipment, $122,580, is included in office furniture and equipment, less applicable depreciation. The lease provides for payments of $1,692 monthly for 120 months to April 26, 1982. The lease liability at June 30, 1972, $121,445, is stated at the discounted present value of the remaining obligation. The lease provides options at the expiration date to renew the lease indefinitely at 1/12 of the present annual rental, to purchase the equipment at 10% of the original cost, to return the equipment to the lessor, or to return the equipment to the lessor as a trade-in on new equipment to be leased. (See Note 2.)

4. COMBINED NET WORTH

The Trustees of the California Medical Association is a wholly-owned subsidiary of the California Medical Association. The Trustees hold in trust a large portion of the assets utilized by the California Medical Association. The combined net worth of the two organizations is summarized as follows:

Entity	June 30 1972	1971	Increase
California Medical Association:			
Restricted as to use	$ 198,120	$ 165,065	$33,055
Unrestricted	290,930	257,875	33,055
	489,050	422,940	66,110
Trustees of the California Medical Association	1,423,264	1,423,264	
	$1,912,314	$1,846,204	$66,110

The combined net worth at June 30, 1972 shown in the summary above does not include the following items:

California Medical Association:	
Excess of the appraised value of furniture and office equipment acquired prior to July 1, 1966 over accumulated depreciation and nominal carrying value, approximately	$ 51,800
Trustees of the California Medical Association:	
Excess of net worth over Trustees' investment in their wholly-owned subsidiary, Pacific Magnetic Tape Equipment Co., based on that company's unaudited balance sheet at June 27, 1972	83,328
	$135,128

5. COMMITMENTS AND CONTINGENT LIABILITY

An antitrust suit against the American and California Medical Associations and others is pending in the Federal District Court in San Francisco. Currently the case is in abeyance pending discussions which involve settlement without any monetary payments. Whether or not settlement is effected, it is the opinion of counsel that California Medical Association will successfully defend itself.

The Association rents its office facilities from Trustees of the California Medical Association for approximately $72,000 per annum. In addition, certain equipment is leased at approximate annual rentals which for the years ended June 30 are as follows: 1973 and 1974—$12,400; 1975—$9,200; 1976—$5,500; 1977—$2,200.

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION
(A Nonprofit Corporation)

Balance Sheet, June 30, 1972 and 1971, and Comparison

	JUNE 30		Increase (Decrease)
	1972	1971	
ASSETS			
CASH:			
Commercial account	$ 1,288	$ 12,985	$ (11,697)
Savings accounts	139,711	112,246	27,465
Total cash	140,999	125,231	15,768
INVESTMENTS IN MARKETABLE SECURITIES, AT COST:			
Certificates of deposit		150,000	(150,000)
U.S. Treasury bonds, 2½%, maturing December 15, 1972 (market value, 1972, $99,500; 1971, $328,247)	100,000	345,000	(245,000)
Corporate fixed income securities (market value, 1972, $311,062; 1971, $276,126)	301,719	278,843	22,876
Listed common stocks (market value, 1972, $663,351; 1971, $423,137)	663,586	442,128	221,458
Total investments in marketable securities	1,065,305	1,215,971	(150,666)
INVESTMENTS IN WHOLLY-OWNED SUBSIDIARIES, AT COST (Note 1):			
Pacific Magnetic Tape Equipment Co.	9,000	9,000	
Six Ninety Three Sutter Publications, Inc.	1,000	1,000	
Total investments in wholly-owned subsidiaries	10,000	10,000	
ACCRUED INTEREST AND DIVIDENDS	6,321	6,991	(670)
PROPERTIES, AT COST (Note 2):			
Buildings and improvements	413,578	407,303	6,275
Carpets, installation, and other	21,029	20,593	436
	434,607	427,896	6,711
Less accumulated depreciation	147,423	143,461	3,962
	287,184	284,435	2,749
Land	180,217	180,217	
Properties, net	467,401	464,652	2,749
EQUIPMENT, AT NOMINAL VALUE	1	1	
CASH SURRENDER VALUE OF LIFE INSURANCE (Note 3)	67,940	62,275	5,665
ACCRUED REAL ESTATE TAXES (contra)	25,000	25,000	
PREPAID INSURANCE AND OTHER EXPENSES	2,231	2,345	(114)
	$1,785,198	$1,912,466	$ (127,268)
LIABILITIES			
ACCOUNTS PAYABLE AND ACCRUED EXPENSES:			
Audio-Digest Foundation	$ 5,646	$ 115,842	$ (110,196)
California Medical Association	35,072	16,138	18,934
Due for securities purchased		18,510	(18,510)
Interest and accrued expenses	874	1,658	(784)
Total accounts payable and accrued expenses	41,592	152,148	(110,556)
ACCRUED REAL ESTATE TAXES PAYABLE (contra)	25,000	25,000	
NOTES PAYABLE:			
California Medical Association, payable on demand, with interest at 4% per year—Unsecured	125,000	125,000	
The Connecticut Mutual Life Insurance Company, with deed of trust as collateral (payable in quarterly installments of $2,506, including interest at 4¼% per year, to December 1, 1973) (Note 2)	4,450	14,029	(9,579)
Total notes payable	129,450	139,029	(9,579)
TRUST FUNDS (Note 3)	164,502	172,510	(8,008)
DEFERRED INCOME	1,390	515	875
EXCESS OF ASSETS OVER LIABILITIES:			
Balance, beginning of year	1,423,264	1,423,171	93
Excess of income over expenses for the year before transfer to California Medical Association	21,458	93	21,365
Transfer to California Medical Association	(21,458)		(21,458)
Excess of income over expenses for the year		93	(93)
Balance, end of year	1,423,264	1,423,264	
	$1,785,198	$1,912,466	$ (127,268)

See notes to financial statements.

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

Statement of Income and Expenses Years Ended June 30, 1972 and 1971 and Comparison

	YEAR ENDED JUNE 30		Increase (Decrease)
	1972	1971	
INCOME:			
Net income from rental properties	$ 15,168	$ 17,848	$ (2,680)
Interest	35,181	35,781	(600)
Dividends:			
Listed common stocks	18,471	1,108	17,363
Pacific Magnetic Tape Equipment Co.	1,800	1,800	
(Loss) on sale of investments	(13,034)	(29,264)	16,230
	57,586	27,273	30,313
EXPENSES (OTHER THAN PROPERTY)—PROFESSIONAL FEES, INSURANCE, AND MANAGEMENT	30,162	18,037	12,125
	27,424	9,236	18,188
OTHER CHARGES—PROVISION FOR RETIREMENT OR OTHER BENEFITS OF EMPLOYEES OF AN AFFILIATED ORGANIZATION	5,966	9,143	(3,177)
EXCESS OF INCOME OVER EXPENSES BEFORE TRANSFER TO CALIFORNIA MEDICAL ASSOCIATION	21,458	93	21,365
TRANSFER TO CALIFORNIA MEDICAL ASSOCIATION	21,458		21,458
EXCESS OF INCOME OVER EXPENSES	$	$ 93	$ (93)

See notes to financial statements.

Notes to Financial Statements

NOTE:

1. WHOLLY-OWNED SUBSIDIARIES OF TRUSTEES

Trustees of the California Medical Association owns all of the outstanding stock of the Pacific Magnetic Tape Equipment Co., which was formed for the purpose of merchandising magnetic tape equipment as an adjunct to the activities of the Audio-Digest Foundation.

Trustees also own all of the outstanding stock of Six Ninety Three Sutter Publications, Inc.

2. PROPERTIES

The properties held by Trustees of the California Medical Association are summarized as follows:

	693 Sutter Street	679 Sutter Street	Total
Buildings and improvements	$335,690	$ 77,888	$413,578
Carpets, installation, and other	20,359	670	21,029
	356,049	78,558	434,607
Less accumulated depreciation	124,953	22,470	147,423
	231,096	56,088	287,184
Land	87,400	92,817	180,217
	$318,496	$148,905	$467,401

The property located at 693 Sutter Street, San Francisco, is subject to a deed of trust to The Connecticut Mutual Life Insurance Company as collateral for a note with a balance of $4,450 at June 30, 1972.

The management decided in 1971 to discontinue recording depreciation on the 693 Sutter Street building, which is used almost entirely by the California Medical Association. Proper maintenance is expected to keep the building in good condition.

The 679 Sutter Street building and improvements are being depreciated over 20 years and carpets, installation, and other property over 10 years. The straight-line method is used.

Appraisals made by Marshall and Stevens on October 15 and December 4, 1970 show the following valuations for the buildings:

	693 Sutter Street	679 Sutter Street
Reproduction cost	$696,618	$277,204
Depreciated reproduction cost	$487,633	$184,639

3. TRUST FUNDS

These funds are summarized as follows:

For Mr. and Mrs. Ben H. Read		$ 69,000
Morris Herzstein Bequest (accumulated earnings remitted to Trustees of the California Medical Association)		7,433
Life insurance retirement plan for legal counsel		67,940
Other:		
Howard Hassard — Deferred compensation	$16,000	
Murray Klutch — Funded by payroll deductions	4,129	20,129
		$164,502

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Gram-Negative Bacterial Endocarditis in Narcotic Addicts

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The number of cases of bacterial endocarditis in drug addicts seen at UCLA and Wadsworth Veterans Administration hospitals increased sharply in 1971 over the average of the four preceding years. Enteric Gram-negative bacilli were the infecting organism in three of the seven cases seen in 1971 but were not found in any cases of endocarditis in the 1967-70 period.

Medical treatment of the patients was, in general, unsuccessful in spite of the intensive use of newer antimicrobials active against enteric Gram-negative bacilli. One patient died with fulminant Pseudomonas endocarditis and two others (Pseudomonas and Serratia endocarditis) eventually required operations on the heart before a cure was achieved.

INTRAVENOUS INJECTION OF ILLICIT NARCOTICS has become increasingly prevalent in the United States. Drug addicts are likely to have a variety of medical complications, including bacterial endocarditis.[1] Published reports indicate that the Gram-positive cocci remain the most frequently isolated organisms from cases of endocarditis in addicts.[2,3] However, recent experience in our hospitals suggests that more and more of these cases are caused by enteric Gram-negative bacilli. These organisms are frequently resistant to multiple antibiotics, making medical therapy extremely difficult. This report consists of three case histories of enteric Gram-negative endocarditis in addicts and data comparing the incidence of bacterial endocarditis in the twelve-month period of 1971 with that of the previous four years, 1967 to 1970.

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Clinical Data

All patients were hospitalized either at the UCLA Hospital, a 600-bed university referral center, or the Wadsworth Veterans Administration (WVA), Hospital, a 900-bed general medical and surgical hospital. The patients all had positive blood cultures and signs and symptoms of bac-

terial endocarditis, including evidence of valvular heart disease. We include in our definition of enteric Gram-negative bacilli members of the family Enterobacteriaceae and the genus Pseudomonas.

Summaries of Cases

CASE 1. A 41-year-old man, a heroin addict who had been successfully treated for enterococcal (Streptococcus faecalis) endocarditis of the mitral valve in December, 1968, was admitted to WVA Hospital August 20, 1971, with fever and congestive heart failure. Multiple blood cultures taken at the time of admission grew Pseudomonas aeruginosa. A clinical diagnosis of bacterial endocarditis was made and the patient was initially treated with intramuscular gentamicin in a daily dose of 6 mg per kg of body weight. Intravenous carbenicillin was added at a dose of 36 grams per day with 1 gram of probenecid. He became afebrile and improved clinically. The minimum inhibitory concentrations (MIC) of gentamicin and carbenicillin for the patient's Ps. aeruginosa were 6.25 mcg per ml and 200 mcg per ml respectively. Measured serum levels of these antibiotics were 5.0-7.5 mcg per ml and 100 to 200 mcg per ml respectively. This isolate of Ps. aeruginosa was able to grow in undiluted serum from the patient obtained during therapy. After six weeks of treatment, blood cultures again grew Ps. aeruginosa. The MIC to gentamicin was now 12.5 mcg per ml. In addition, symptoms of mild eighth nerve toxicity appeared. Gentamicin and carbenicillin were discontinued and combined therapy with sulfadiazine, trimethoprim, and polymyxin B was instituted in daily doses of 6.0 grams orally, 960 mg orally and 135 mg intramuscularly, respectively. *In vitro* susceptibility testing had suggested that this combination might be therapeutically effective. The addition of sulfadiazine and trimethoprim appeared to enhance the bactericidal activity of polymyxin B (MIC reduced from 0.75 mcg per ml to 0.2 mcg per ml). The patient was afebrile and asymptomatic for 19 days while receiving this therapy. However, a slight fever then developed and Ps. aeruginosa was recovered from three blood cultures. The triple combination of antimicrobials was therefore stopped and a third treatment program was begun, this time using a combination of tobramycin (nebramycin) and carbenicillin in daily doses of 300 mg intramuscularly and 36 grams intravenously, respectively. The MIC to tobramycin was 6.25 mcg per ml and serum levels of 2.75 to 6.2 mcg per ml were measured. The patient once again became afebrile but showed little clinical improvement otherwise. Therefore, after a further month of medical treatment, cardiac operation was performed with debridement of a vegetation from the mitral valve. Two weeks after operation the patient was discharged from the hospital on no antimicrobial therapy.

CASE 2. A 41-year-old man who was addicted to heroin was successfully treated for tricuspid endocarditis due to Staphylococcus aureus in December, 1970. Subsequently he resumed intravenous heroin use and in April, 1971, chills and fever developed with jaundice and ankle edema. He was admitted to a hospital and a diagnosis of tricuspid valve endocarditis due to Serratia marcescens was made. This original isolate was susceptible to chloramphenicol and gentamicin (MIC for both agents 1.5 mcg per ml). Despite eight weeks of therapy with gentamicin (5.0 mg per kg per day), fever and positive blood cultures persisted. A Serratia isolate obtained at this time was resistant to gentamicin (MIC >25 mcg per ml) and treatment with chloramphenicol intravenously (4.0 grams per day) was begun. A month of this therapy followed by a week of combined gentamicin-chloramphenicol therapy was unsuccessful. A third Serratia isolate was now resistant to all antibiotics in common usage (MIC's to chloramphenicol and gentamicin both >25 mcg per ml). The patient was transferred to the WVA Hospital August 6, 1971, with chills and fever and the murmur of tricuspid valve insufficiency. *In vitro* studies showed that the combination of sulfadiazine, trimethoprim, and polymyxin B was bactericidal for the third Serratia isolate at concentrations within the therapeutic range. Treatment was begun with a combination of sulfadiazine 6.0 grams per day by mouth, trimethoprim 1.0 gram per day by mouth and polymyxin B 120 mgs per day intramuscularly. The patient became afebrile and blood cultures were sterile. This therapy was stopped after eight weeks, and two weeks later a relapse of the infection occurred. The three-drug combination was resumed and again the patient became afebrile and blood cultures were sterile. His general condition progressively improved over the next ten weeks until, rather abruptly, azotemia, hematuria (without crystalluria), eosinophilia, and fever developed. The antimicrobial agents were stopped because of suspected toxicity and blood cultures taken one day later, again grew Serratia marcescens. Gentamicin and chloramphenicol were temporarily re-

instituted and one week later cardiac operation was performed for removal of the tricuspid valve. Cultures of the valve yielded Serratia marcescens. Postoperatively, fever disappeared and blood cultures were sterile.

CASE 3. A 39-year-old woman, a heroin addict, was admitted to the UCLA Hospital August 2, 1971, with a five-day history of chills, fever and painful spots on the arms and legs. Florid lesions of bacterial endocarditis were present, including splinter hemorrhages and Roth spots. There was a loud cardiac murmur of mitral insufficiency, and the spleen was enlarged. The temperature was 40°C (104°F). Microscopic hematuria was present and the cerebrospinal fluid showed pronounced pleocytosis. Nine of ten blood cultures grew Pseudomonas aeruginosa. The patient was treated with a combination of gentamicin and carbenicillin in doses of 4.5 mg per kg per day intramuscularly and 24 gm per day intravenously, respectively. *In vitro* tests with the Pseudomonas isolate demonstrated an MIC of 1.56 mcg per ml for gentamicin and 200 mcg per ml for carbenicillin. Measured peak serum levels for gentamicin were 3.8 to 5.7 mcg per ml and for carbenicillin were 400 to 800 mcg per ml. A 1:16 dilution of the patient's serum obtained during therapy killed a Pseudomonas isolate. Her condition improved slightly at first but then rapidly deteriorated as meningitis, endophthalmitis, and hepatic failure developed. Intrathecal and subconjunctival injection of gentamicin were futile and the patient died on the thirteenth hospital day. A postmortem examination revealed vegetations on the mitral valve.

None of 57 cases of bacterial endocarditis seen at UCLA and Wadsworth hospitals between 1967 and 1970 was caused by enteric Gram-negative bacilli (Table 1). There were three cases of endocarditis in narcotic addicts during this period and all were caused by Gram-positive cocci. One of these cases occurred in 1968 and the other two were in 1970. In contrast, during 1971, there were four cases of endocarditis due to enteric Gram-negative bacilli, three of which were found in narcotic addicts. The fourth was in a patient with a prosthetic heart valve.

Between 1967 and 1970, 57 cases of endocarditis were seen, an average of 14.3 per year. Three of these (5.3 percent) occurred in addicts. In 1971, a total of 29 cases of endocarditis were seen, seven (24 percent) in addicts.

TABLE 1.—*Data on Cases of Bacterial Endocarditis at the UCLA-WVA Hospitals During the Four Years 1967-70 and from January 1, 1971 to December 31, 1971*

	1967-70	*1971*
Total number of cases	57	29
Cases in non-addicts due to enteric Gram-negative bacilli	0	1
Cases in addicts due to enteric Gram-negative bacilli	0	3
Cases in addicts due to Gram-positive cocci	3	4
Total number of cases in addicts	3	7

Discussion

Cherubin and Neu[4] observed an increase in the association of narcotic addiction with endocarditis, from 0.4 percent in 1948-57 to 3.9 percent in 1958-67. An average of 5.3 percent of the cases of bacterial endocarditis seen at UCLA-WVA hospitals from 1967-70 occurred in addicts. In 1971 it was 24 percent. These data suggest that narcotic addiction as a cause of endocarditis is increasing in importance and that this increase has occurred quite recently. In fact, of the ten cases of endocarditis in addicts treated in our hospitals since 1967, nine were seen in 1970 and 1971. Moreover, this increase has contributed significantly to a 100 per cent increase in the incidence of all cases of bacterial endocarditis at UCLA-WVA hospitals.

Previous reports emphasize the importance of Gram-positive cocci in addict endocarditis. Ramsey et al[3] noted only seven of 93 cases (7.5 percent) due to enteric Gram-negative bacilli. Cherubin et al[2] and Louria et al[5] reported an incidence of 13.5 percent and 15 percent, respectively. Our data from 1967 to 1970 reveals no cases of Gram-negative endocarditis. However, in 1971 three of seven cases (43 percent) were caused by these organisms. This experience at UCLA-WVA hospitals suggests that enteric Gram-negative bacilli are of increasing importance in the etiology of addict endocarditis.

There are probably multiple reasons for an increase in Gram-negative endocarditis in addicts. Two of our three patients had had previous episodes of Gram-positive endocarditis. They required extensive stay in hospital and were treated with prolonged courses of antibiotics that were inactive against Gram-negative bacilli. Moreover, many addicts spend considerable time in hospital for treatment of other complications of addiction. This experience indicates ample opportunity for

colonization with antibiotic-resistant enteric Gram-negative bacilli. These organisms, including Pseudomonas and Serratia, are recognized as frequent contaminants of the hospital environment and as the causes of many nosocomial infections.[6] Once colonization has occurred, repeated non-sterile intravenous injections offer a ready pathway into the addict's bloodstream.

Our third patient (who had Pseudomonas endocarditis) had not been ill or in hospital previously. However, since addicts commonly share their intravenous equipment,[7] Pseudomonas may have been acquired from another "hospital-colonized" addict. Moreover, the frequent practice of diluting the narcotic with ordinary tap water, toilet bowl water, or commercial "purified" drinking water is another possible source. Pseudomonas, in particular, is able to survive in moist environments such as sink traps and faucet filters.[8,9]

The failure of intensive treatment of our three patients with various antimicrobial agents serves to reinforce the impression that Gram-negative endocarditis seldom is cured by medical therapy alone.[3,10,11] Cures have been recorded in cases where simple debridement of vegetations or valvulectomy (with or without prosthetic valve replacement) have been combined with antimicrobial therapy.[12,13] In Case 1 herein reported, Pseudomonas endocarditis was cured only after debridement of the mitral valve and in Case 2 the patient (who had Serratia endocarditis) eventually required resection of the tricuspid valve.

Although medical therapy was not totally effective in our patients, suppression of bacteremia was achieved, enabling them to improve so that chances for surviving cardiac operation were greatly enhanced. The combination of gentamicin and carbenicillin was used in Case 1 because of the frequent synergistic activity of these agents against Pseudomonas.[14,15] However, this therapy alone was not curative, and in Case 3 also it was ineffective in controlling fulminant endocarditis. Tobramycin, a new aminoglycoside antibiotic reported to have enhanced activity against Pseudomonas,[16] was also used in Case 1. Although the MIC to tobramycin was relatively high, this agent, in combination with carbenicillin, appeared to control the bacteremia.

The Serratia marcescens recovered from the patient in Case 2 sequentially developed resistance to gentamicin and chloramphenicol, the only antimicrobial agents to which it was originally susceptible. This led to the use of the combination of polymyxin B, sulfadiazine and trimethoprim. The latter two agents act synergistically and have been used together in a variety of infections.[17,18] It has been suggested that combining either a sulfonamide or trimethoprim or both with a polymyxin results in additional synergistic activity against a number of Gram-negative bacilli.[19-22] During therapy with such a triple combination, the patient in Case 2 was abacteremic and clinically improved. However, it is clear from the early relapse after discontinuation of treatment that this regimen had not cured the Serratia endocarditis. Moreover the triple combination, when used in Case 1, suppressed the bacteremia for only 19 days. Although these newer antimicrobial agents have been of some benefit, our experience suggests that they are not curative in Gram-negative bacterial endocarditis.

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Life-Threatening Dermatoses

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Four life-threatening dermatoses—Stevens-Johnson syndrome, toxic epidermal necrolysis, Kaposi's varicelliform eruption and purpura fulminans—are unique in their abrupt onset and rapid progress to death, but prompt diagnosis and proper therapy can often cure the condition or prevent undesirable sequelae. Since two of the four conditions can follow the use of a variety of drugs and all may be secondary to an infectious agent, any physician may encounter them in practice and should be aware of their seriousness.

MODERN THERAPY has so changed the course of many fatal dermatoses, such as pemphigus vulgaris, that now patients may die from the complications of therapy rather than from the disease itself. In dermatoses such as generalized exfoliative dermatitis, where etiologic factors may be obscure, the cause of death is frequently difficult to assign, although in some patients it may be high output cardiac failure, particularly in those with underlying heart disease.[1]

A discussion of all the potential life-threatening dermatoses is beyond the scope of this paper and many represent the cutaneous component of a more serious systematic disease, as in systemic lupus erythematosus, dermatomyositis, periarteritis nodosa, and malignant atrophic papulosis of Degos. There are also several fatal congenital disorders such as epidermolysis bullosa letalis, as well as certain serious mycobacterial and fungal infections.

This discussion is limited to four different and distinct life-threatening dermatoses: Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Kaposi's varicelliform eruption (KVE) and purpura fulminans. These four are unique in that they are always abrupt in onset and can swiftly progress to death. Most important, prompt diagnosis and proper therapy can often cure the condition or prevent undesirable sequelae.

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Stevens-Johnson Syndrome

Stevens-Johnson syndrome is usually classified as a serious variant of bullous erythema multiforme.[2] It ordinarily affects children and young adults. Its abrupt onset is heralded by high fever, headache, painful erosions about the lips and in the mouth, and bilateral conjunctivitis (Figures 1 and 2). A vesiculo-bullous eruption, often with the typical iris or target lesion, develops on the skin (Figure 3). The course is stormy, with many signs of toxicity, and bronchial pneumonia may develop as a complication. The death rate in patients with this syndrome is 10 to 25 percent.[3]

Mucosal lesions occur in all patients, regardless of the severity, and this finding, plus the typical cutaneous lesions, should make the diagnosis readily apparent. Serious ocular involvement is a dreaded complication since it can result in partial or total blindness.[4] Duration of the disease is



Figure 1.—Erosive lesions of lips and tongue in patient with Stevens-Johnson syndrome.



Figure 2.—Bilateral conjunctivitis in patient with Stevens-Johnson syndrome.

ordinarily four to six weeks but severe cases may last two or three months.

Stevens-Johnson syndrome may occur in association with systemic infection, pregnancy, foods, deep x-ray therapy, and neoplasms.[5] Of the viruses herpes simplex and adenoviruses are the most frequent causative agents.[6] It is also probably the most common severe drug eruption, with a great number of drugs implicated—penicillin, sulfonamides, antipyrine, phenylbutazone, the anticonvulsants and others. The most frequent etiologic drugs are reported to be the long-acting sulfonamides, especially sulfamethoxypyridazine.[2] Mounting evidence in recent literature also indicates that the mycloplasma organisms are not infrequent causative agents. Ludlam and associates[7] found raised titers of complement fixative antibody to mycoplasma in four out of five cases of Stevens-Johnson syndrome; and Lyell and associates[8] isolated mycoplasma pneumonia from blister fluid and material from the throats of patients with erythema multiforme.



Figure 3.—Target lesions of erythema multiforme as seen in Stevens-Johnson syndrome.

Treatment consists of prompt admission to hospital, nursing care, systemic corticosteroids and the use of broad spectrum antibiotics, especially if mycoplasma infection is discovered. Significant eye involvement requires ophthalmologic consultation and the topical use of corticosteroids. Even with massive doses of corticosteroids, new lesions may appear and the disease may worsen. Renal involvement with hematuria or even renal tubular necrosis has been reported, and these conditions may progress to renal failure.[9,10]

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) first became recognized as a distinct entity after Lyell's description of the disease in 1956.[11] Lyell used the word *toxic* to express the acute damage to the epidermis. Since 1956 about 400 cases of this syndrome have been reported and an analysis of them reveals that the disease has many causes and variable prognosis.[12] The typical clinical description and course of the disease in the young is exemplified by the following case:

The patient, a three-year-old boy, first became ill in January 1967 and his mother noted the sudden onset of redness about the face and trunk in association with exquisite tenderness of the skin. He had had a low-grade fever for the previous 24 hours, for which the mother had given aspirin tablets, totaling approximately four. Within a few hours the erythema progressed about the face and became especially pronounced in the flexural skin areas. The scalp remained uninvolved. The patient was admitted to the hospital two days after onset of the illness, at which time he was anorectic and in distress from painful skin. Desquamation had

begun in the areas of the upper back and the Nikolsky sign was present. Except for the skin changes and a few blisters about the lips, no abnormalities were noted on physical examination and there was no elevation of temperature. Leukocytes numbered 4,800 per cu mm with normal differential except for 8 percent eosinophils. Hemoglobin content and results of urinalysis were normal as were cultures of the blood and throat. Nasal cultures revealed coagulase-positive Staphylococcus aureaus, phage type 71.

The child was admitted to isolation and reverse isolation and high doses of penicillin were started. Intravenous fluids were given for the next three days since painful blisters about the lips and mouth prevented oral ingestion. By the third hospital day definite desquamation of the epidermis from the most erythematous areas of the back, chest, ears, neck and hands had begun (Figures 4 and 5). The pain, erythema and facial edema improved decidedly after only 24 hours of treatment, and by the fifth hospital day the condition was resolving rapidly. The child was discharged from the hospital on the eleventh day completely well and with only mild erythema of the previously desquamated areas. He remained free of disease on follow-up examinations.

This is the typical history of a young patient with TEN. The characteristic features are the abrupt onset, exquisite skin tenderness, erythema which is most pronounced on the face and flexural areas, typical burn-like desquamation (hence the term "scalded skin syndrome"), and the usual 10- to 14-day course with complete recovery.[13] A short prodrome of malaise, lethargy and fever may precede the disease, but once the erythema appears the disease becomes explosive. When death occurs it is usually within the first five to eight days. Laboratory investigations of the blood are usually not informative although leukocytosis and leukopenia have both been reported.[14] Histologically there is necrosis of the superficial layers of the epidermis with a striking absence of inflammation.[11]

A symposium on TEN was held in Munich in November 1969.[15] From the reports given, it is clear that there are many causes of the syndrome and that the condition in children shows many differences from that in adults. In the adult type, components of Stevens-Johnson syndrome are frequently associated both histologically and clinically and indeed not only can differential diagnosis be difficult but both syndromes may occur



Figure 4.—Desquamation and suppuration from areas of previous erythema and tenderness (TEN).



Figure 5.—Patient with TEN on third hospital day of therapy.

in the same patient at the same time. I recently observed such a patient whose eruption was secondary to administration of ampicillin.

The childhood variety of TEN is thought to be due in almost all instances to infection of the skin, throat or elsewhere with staphylococcus Group 2, phage type 71, thus linking this disease with Ritter's disease of the newborn.[13,16,17] The childhood variety has now been referred to as Ritter von Rittershain-Lyell's disease.[17] The syndrome in children can be caused by other bacteria, however, and is thought by some investigators to be a rare manifestation of the exanthems.[13]

Arbuthnott and associates[18] showed that the



Figure 6.—Localized areas of TEN in a child treated with sulfadiazine for an upper respiratory infection.

staphylococci isolated from cases of TEN produce a major identifiable exotoxin not present in staphylococci isolated from cases of impetigo. Melish and Glasgow[19] and Arbuthnott and associates[20] recently reproduced the disease experimentally by injecting newborn mice with Group 2 staphylococci isolated from cases of TEN. The characteristic exfoliation occurs only in mice less than seven days of age. Fluid aspirated from the bullae were repeatedly sterile, which is consistent with the observations in clinical reports of TEN and suggest that a soluble product such as exotoxin induces the dermatologic manifestations of the disease. This factor is elaborated from a focus of staphylococcus infection elsewhere in the body. It is then disseminated to produce erythema, tenderness, intraepidermal separation and exfoliation. It was also found that the newborn mice had an inadequate inflammatory response to the effective doses of staphylococci and this appears to provide optimum conditions for the growth of bacteria and the production of the toxin. The nature of the soluble blister-producing substance has not yet been defined but it is non-dialysable and is thermolabile, suggesting that it is a macromolecular product of Staphylococcus aureus and not a metabolite of small molecular weight.[20] In the experimental model, as well as apparently in humans, susceptibility to this necrolytic factor seems to decrease with age.

Recurrences of TEN in children are unusual, the outlook is good, mortality rate is low and complications few.[13] The desquamation that follows the uncommon entity of staphylococcal scarlet fever is probably a mild example of TEN.[21] Minor, localized, necrolytic skin reactions can also occur after the use of drugs and may be overlooked (Figure 6). In such cases the reexposure to the offending drug may evoke the disease, with serious sequelae. Other less common causes of the disease in children are immunizations and boric acid intoxication.[16]

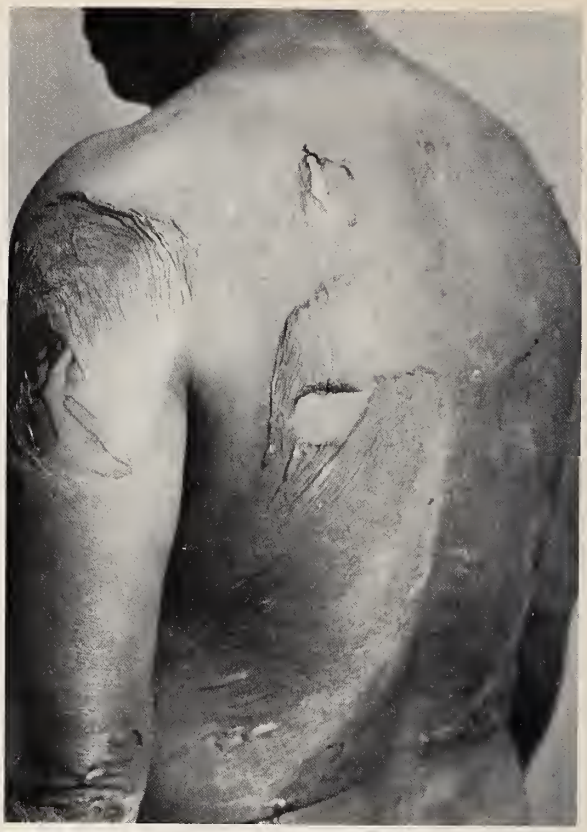


Figure 7.—Large areas of desquamation (TEN) in a patient following drug therapy. Patient died of the disease after a second exposure to the offending drug. (Patient seen at U.S.P.H. Hospital, San Francisco)

The adult variety of TEN is in many instances due to drugs, the most frequent etiologic agents being phenylbutazone, anticonvulsants, and the sulfonamides[16] (See Figure 7). Recurrences are common in adults, especially if the offending drug is given again. In drug-induced TEN, little is known about the pathophysiology, but it does not seem to be a manifestation of either the Sanarelli-Shwartzman reaction or the Arthus phenomenon.[15] There is also an idiopathic form of the disease which occurs especially in middle-aged women and carries a mortality rate of 50 percent.[15] Adult patients with this idiopathic form are also prone to recurrent attacks should they survive the initial

episode. Schuppli,[22] collecting reports of 314 cases of TEN from the literature between 1962 and 1968, found an overall mortality rate for adults of about 40 percent. As indicated, the best prognosis appears to be in the childhood variety, although in children less than one year of age the mortality rate has been reported to be 33 percent.[13]

The prognosis of TEN is to a large extent dependent upon adequate nursing care. The patient should be nursed in as aseptic conditions as possible, and general treatment should follow the rules of burn therapy. Birke and associates[12] recently successfully treated five patients with advanced manifestations of TEN in an atmosphere of warm, dry air throughout the acute phase. This treatment appears to eliminate the need for topical antibacterial therapy. Systemic antibiotics are essential in the childhood cases secondary to Staphylococcus aureus and are often indicated in adults. The role of corticosteroid therapy is not yet clear but some investigators are of the opinion that corticosteroids given in high doses early in the course of the disease are of definite therapeutic benefit.[12,13,22]

Kaposi's Varicelliform Eruption

Kaposi's varicelliform eruption (KVE) is an acute viral infection superimposed upon chronic dermatosis. Either the herpes simplex virus or the vaccinia virus is the etiologic agent and, depending upon the causative virus, the infection is designated either eczema herpeticum or eczema vaccinatum. More recently the Coxsackievirus A16 was implicated as another possible cause of the disease.[23] The underlying dermatitis is most commonly atopic eczema but the disease can occur in seborrheic dermatitis, Darier's disease, ichthyosis, contact dermatitis, pemphigus, acne, scabies, impetigo, secondary syphilis and in the Wiscott-Aldrich syndrome.[24-27] KVE is the main reason to avoid smallpox vaccinations in patients with eczema or a past history of eczema, eczema affecting a household member, or any active skin disorder. Clinically the lesions and symptoms produced by the herpes simplex are often indistinguishable from those of the vaccinia virus, but the history of exposure and laboratory studies can aid in differentiation. This differentiation is often of great importance, not only as to the choice of therapy but as to prognosis also, since herpes simplex, once established, can be recurrent whereas vaccinia without further exposure is not. Recurrent attacks of KVE due to herpes simplex virus tend to be less severe than the primary episode and may occur on atopic skin after the eczema has disappeared.[28]

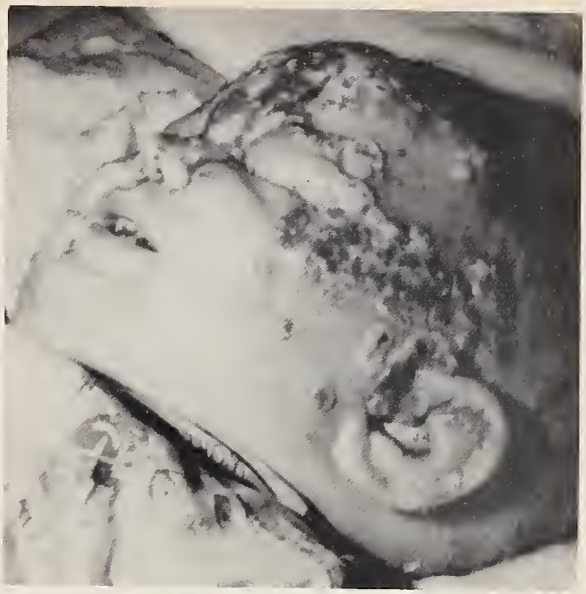


Figure 8.—Eczema vaccinatum

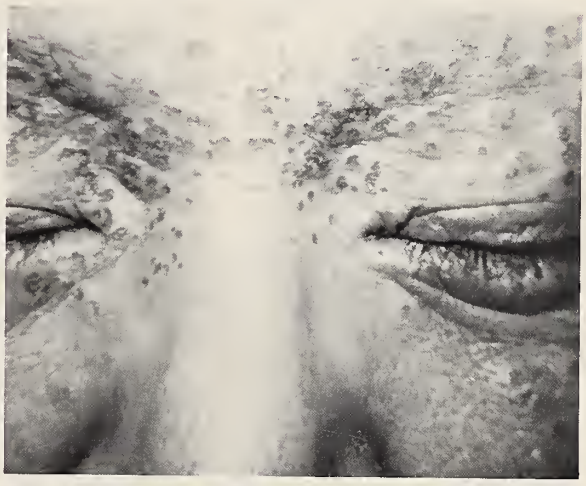


Figure 9.—Eczema herpeticum

The vesicles appear abruptly as a succesion of crops both in and about the diseased skin and they continue to erupt over a period of a week. The vesicles frequently become confluent and pustular and regional lymphadenopathy appears (Figures 8 and 9). Ocular keratitis is a frequent complication, especially when the face is involved. Fever and toxic symptoms may occcur and in the extensive case the patient is seriously ill. Viremia with viral infection of internal organs accounts for some of the fatalities as does secondary bacterial septicemia.[29]

Recent surveys show that about 125 cases of



Figure 10.—Multiple areas of purpura 48 hours after onset of purpura fulminans. (From: Cram and Soley.[42])

eczema vaccinatum occur each year in the United States, usually in patients with atopic eczema.[30] Eczema vaccinatum used to be fatal in 30 to 40 percent of children and about 6 percent of aduts before the development of vaccine immune globulin (VIG).[31] Epidemics occurred after mass vaccination campaigns, as in May 1947 when 43 cases were reported in New York City alone.[32] VIG is hyperimmune gamma globulin prepared from the blood of United States Armed Forces personnel recently vaccinated against smallpox and is distributed by American Red Cross centers across the United States. The present recommended dose of VIG is 0.6 ml per kg of body weight given intramuscularly in divided 10 ml amounts every four hours until total dosage is achieved.[33] It has significantly reduced mortality in children, as was shown in a recent study by Kempe of 132 cases, in which the death rate fell to 7 percent.[34] VIG theoretically terminates viremia and prevents further spread of skin lesions by producing neutralizing antibodies which otherwise appear late in the eczema vaccinatum patient.

The thiosemicarbazones, antiviral compounds reported successful in the treatment of cases of variola and severe vaccinal complications, may eventually prove to be the therapeutic drugs of choice.[35] Methisazone, a thiosemicarbazone drug, has not yet been approved for marketing in the United States but is available for general use in Great Britain. It is given orally with an initial loading dose of 200 mg per kg of body weight followed by 400 mg per kg in divided doses over a total of 48 hours. The most prominent side effects are nausca and vomiting, which may be partially controlled by the use of antiemetics.[35,36]

Eczema herpeticum can be more difficult to treat. The administration of gamma globulin in amounts to provide sufficient levels of neutralizing antibodies immediately after onsent of the primary herpetic infection has been used to try to prevent viremia and systemic spread of the virus, but this has been of little value once the infection is established or in recurrent disease.[28] Wet compresses and the use of antibiotics in the event of secondary infection are the primary forms of therapy. Idoxuridine (Dendrix,® Herpex® or Stoxil®) should be used in the eyes if herpes keratitis appears.[37] I have also used idoxuridine on the skin in cases of eczema herpeticum, with significant benefit.[38] Prevention is the best therapy for KVE, especially in the case of eczema vaccinatum, where more careful screening of patients for the known contraindications to vaccination should be stressed.

Purpura Fulminans

Purpura fulminans is a severe, rapidly fatal illness which occurs most often in the young.[39] The disease is characterized by the abrupt appearance of large areas of cutaneous hemorrhage and gangrene during the convalescent period of various bacterial and viral infections. Intravascular occlusions with ischemia and localized areas of massive ecchymosis are associated with chills, fever, prostration and rapid progression to hemorrhagic shock, coma, and finally death. In the cases reported more than 90 percent of the patients died and the survivors usually lost digits or limbs during the process.[40,41] In this disease, more than any of the others, prompt diagnosis and adequate therapy is paramount to saving life. This is exemplified by the following case, which was previously reported elsewhere.[42]

The patient, a five-year-old Negro girl was admitted to hospital on 14 February 1967 with a 48-hour history of fever, myalgia, listlessness and generalized progressive purpuric skin eruption. Diagnosis before admission was meningitis, and the patient had been given aqueous penicillin 1,000,000 units intravenously, hydrocortisone, sulfadiazine and intravenous fluids. Because of shock she had also been given a blood transfusion and intravenous levarterenol (Levophed®). On admission she was extremely ill. Bilateral conjunctival hemorrhage, edema of face and extremities, and wide areas of ecchymosis were noted (Figure 10). Leukocytes numbered 15,400 per cu mm with a



Figure 11.—Areas of gangrene and eschar formation in patient with purpura fulminans.



Figure 12.—Residual deformities of feet in patient with purpura fulminans. Right foot was later amputated. (From: Cram and Soley.[42])

shift to the left in the differential, and platelets 80,000. Bleeding time, partial thromboplastin and prothrombin time were prolonged. Results of spinal fluid examination were within normal limits and cultures of this fluid and the blood were negative.

A diagnosis of purpura fulminans was made and treatment was started immediately with heparin. The penicillin and hydrocortisone were continued and the child was also treated with 250 ml of low molecular weight dextran on the first, third and fifth day. Over the next 48 hours many of the ischemic areas improved and the patient became more responsive. Large bullae appeared over many of the purpuric areas, as well as gangrene of several digits and the less viable ecchymotic skin (Figure 11). By the seventh hospital day the child was decidely improved and the leukocyte and platelet counts and prothrombin time had returned to normal. The heparin and dextran were stopped and careful daily debridement of the necrotic skin areas was begun. On 9 March 1967 the patient was transferred to a plastic surgery service for further corrective operation. She underwent six operations for debridement with skin grafts to the left forearm, both legs and both feet. Amputation of the right foot was later necessary (Figure 12).

The cause of purpura fulminans has not been fully established but the presence of perivascular inflammation and intravascular thrombosis has prompted most observers to consider it analogous to the generalized Shwartzman phenomenon which can be experimentally demonstrated in laboratory rabbits.[43,44] The primary pathologic event in the affected person is disseminated intravascular coagulation (DIC), the hemostatic hallmarks of which are the depletion of platelets, fibrinogen, prothrombin, factor V, factor VIII and the activation of the fibrinolytic enzyme system.[45] McKay also demonstrated the appearance of an anticoagulant (antithrombin) in purpura fulminans.[46]

Many infectious organisms and disease states have been associated with DIC.[47] One of the fundamental biological properties of certain viruses is their ability to trigger the blood-clotting mechanisms *in vivo*.[48] Probably minor degrees of intravascular clotting occur in several viral disorders such as varicella, rubella and rubeola, but only on very rare occasions does the explosive and life-threatening form of purpura as described herein occur. McKay emphasized that DIC may be quite extensive or severe without the development of occlusive thrombi.[48] DIC may also follow bacterial septicemia, the prototype of which is meningococcemia. Here, however, the skin purpura rarely results in extensive necrosis, mucous membrane bleeding is common and signs of meningitis plus positive blood and spinal fluid cultures for the meningococcus are the diagnostic features.

Until rather recently most patients with purpura fulminans were treated with a combination of anticoagulants, antibiotics and corticosteroids,[49] and occasionally low molecular weight dextran was used.[50] Since a fundamental pathogenic mechanism of purpura fulminans is DIC, anticoagulants such as heparin are now the therapeutic agents of choice.[48] The beneficial effect of heparin is exerted through its antithrombin activity and direct prevention of further thrombosis. The therapeutic

use of anticoagulants has been life-saving in several recently reported cases of purpura fulminans.[41,45,51] Treatment must be begun promptly since most deaths occur in the first 48 to 72 hours and heparin sodium does not affect capillary thrombi already formed.[45] The recommended dosage of heparin is 100 units (1 mg) per kg of body weight given intravenously every 4 to 6 hours until coagulation functions in preheparin plasma samples and the platelet counts have stabilized to normal levels.[51] Most of the hemostatic mechanisms recover very rapidly, often within 48 hours, but since the platelet count may not return to normal for several days, heparin must not be discontinued prematurely.

Since necrotic lesions resembling purpura fulminans are seen in other conditions not involving intravascular clotting, a diagnosis of consumption coagulopathy must be reliably confirmed before heparin is given.[52] In hospitals not having facilities for complete coagulation study, minimum studies should include a platelet count and determination of plasma prothrombin, partial thromboplastin and thrombin clotting times.[51]

Epsilon-amino-caproic acid has been recommended for the latter phases of this disease[48,52] but the role of fibrinolysis in purpura fulminans and thus the use of this agent that inhibits fibrinolysis is not well defined as yet. More studies are needed before the value of this other therapeutic agent can be adequately assessed.

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Pelvic Exenteration

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Pelvic exenteration offers the only possibility for cure in patients who have pelvic recurrence after receiving optimum amounts of irradiation. With improved radiotherapy techniques, the number of patients with isolated central failure is steadily diminishing, but there remains a significant number of patients with recurrent cancer of the cervix after radiation therapy for whom the procedure offers the only chance for life. Each patient must be assessed individually, with the risks of the procedure weighed against the possible benefits. Technical advances continue to reduce the operative mortality and ameliorate the postoperative morbidity associated with pelvic exenteration.

EXTENDED OR ULTRA-RADICAL SURGICAL OPERATION in the treatment of advanced and recurrent pelvic cancer is an American invention made possible by advances in the ancillary sciences which support the surgical team. The natural history of many pelvic cancers is such that they may be locally advanced but still limited to the pelvis. Thus, unlike most other malignant lesions, they lend themselves to radical resection. Brunschwig[1] in 1948 introduced the operation of pelvic exenteration or cancer of the cervix. Since that time an extensive experience with pelvic exenteration has been accumulated and the techniques as well as patient selection have steadily improved so that now, 25 years later, this procedure has attained an important role in the treatment of gynecologic malignant disease. Pelvic exenterative operation, severely criticized at first, is now accepted as a respectable procedure that can offer life to selected patients when no other possibility of cure exists. The criticism of this procedure has been lessened by the steadily improving mortality and morbidity rates and the gratifying five-year survival record. Most important, however, it has been shown that patients who survive this procedure can be rehabilitated to a useful and healthful existence.

Although pelvic exenteration has been used for a variety of pelvic malignant lesions, its greatest and most important role is in the treatment of

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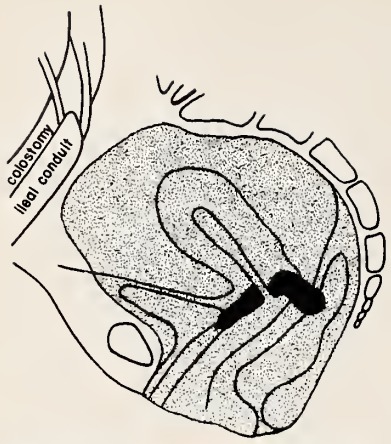


Figure 1.—Total exenteration with removal of pelvic viscera including bladder and rectosigmoid flexure.

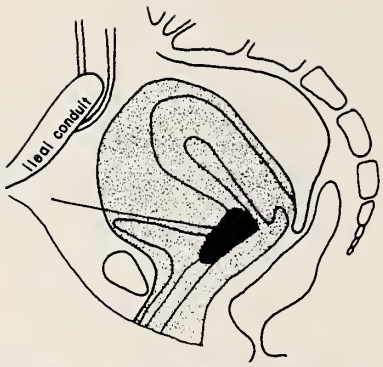


Figure 2.—In selected cases the procedure may be limited to anterior exenteration with the removal of bladder and preservation of the rectosigmoid flexure.

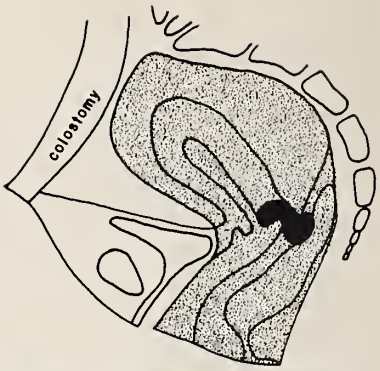


Figure 3.—Posterior exenteration, also for selected cases, with the rectosigmoid flexure removed and the bladder preserved.

advanced or recurrent carcinoma of the cervix. Total exenteration with removal of the pelvic viscera, including the bladder and rectosigmoid flexure, is the procedure of choice for carcinoma of the cervix recurrent or persistent within the pelvis after irradiation (Figure 1). In very selected cases the procedure may be limited to either an anterior exenteration with removal of the bladder and preservation of the rectosigmoid flexure (Figure 2); or posterior exenteration with removal of the rectosigmoid flexure and preservation of the bladder (Figure 3). Cogent objections have been raised regarding these limited operations, especially in patients with carcinoma of the cervix recurrent after irradiation, because of the increased risk of an incomplete resection. In addition, patients in whom the bladder or rectum is preserved often are victims of multiple complications and malfunctioning of the preserved organ. Consequently, some surgeons have abandoned subtotal exenteration.

One of the greatest technical advances in the evolution of pelvic exenteration is the intestinal conduit for diversion of the urinary stream. Originally Brunschwig transplanted the ureters into the left colon just proximal to the site of colostomy, creating the so-called "wet colostomy." The complication rate from this procedure, especially electrolyte imbalance and severe urinary tract infections, was unacceptable. We are indebted to Bricker[2] for popularizing the use of and ileal segment conduit for urinary diversion. The incidence of both postoperative pyelonephritis and hypochloremic acidosis has been greatly reduced. Furthermore, the patients are dry and comfortable and, therefore, more easily rehabilitated. More recently, a segment of sigmoid colon rather than small bowel has been utilized by some surgeons in selected cases as a urinary conduit. This technique offers the additional advantage of avoiding small bowel anastamosis and the threat of fistula formation attending it.

Patient Selection

Only a small portion of the patients with recurrent cancer of the cervix are suitable for this operation. Metastatic extension outside the pelvis, whether manifest before operation or discovered at laparotomy is an absolute contraindication to pelvic exenteration. The triad of homolateral leg edema, sciatic pain and ureteral obstruction is pathognomonic of recurrent and unresectable disease in the pelvis.[3] The triad must be complete, however, to be entirely reliable. Weight loss, cough, anemia and other aberrations suggestive of advanced disease are not sufficient justification of themselves to discontinue efforts toward surgical management. Obesity, advanced age and systemic diseases may interdict extensive operation, in direct relation to the severity of these factors. Some patients are unsuitable for psychiatric reasons and a number of women, otherwise candidates for pelvic exenteration, decide to accept the risk of recurrence without resection.

While the pelvic examination plays a key role in the preoperative assessment of individual pa-

tients, the examiner's impression of resectability must be tempered by the knowledge that errors are common. A small central lesion with freely mobile parametria reliably demonstrates resectability; however, immobility can be due to radiation fibrosis or to pelvic inflammatory disease (old salpingitis, inflammation from uterine perforation and the like). Consequently, even when the disease seems inoperable on pelvic examination, if other factors are favorable one should proceed with the investigation and exploratory laparotomy to avoid the error of a premature decision. Obviously in many cases the finest clinical judgment must be used to avoid rejecting a potentially curable patient, and also to prevent as often as possible subjecting an unsuitable patient to the rigors, fears and false hopes of prolonged preparation for a fruitless operation.

Evaluation studies before operation include chest x-ray studies, an intravenous pyelogram, creatinine determination, liver function tests and an assessment of the patient's hemostatic mechanism. Bilateral lower extremity lymphography has been useful in the experience of some surgeons. Bone survey and liver scan are not part of the "routine" evaluation. A blind scalene node biopsy has been advocated by Ketcham[4] and, if positive, would be a contraindication to further operation.

At laparotomy the entire abdomen and pelvis are explored for evidence of metastatic and intraperitoneal cancer. The lymph nodes around the lower aorta become the first area of sampling if the exploration of the abdomen has revealed no evidence of disease. The patient probably has had a lymphangiogram before laparotomy, which is helpful in directing the surgeon to suspicious nodes in the para-aortic and pelvic area. If the lower aortic area is negative, bilateral pelvic lymphadenectomy is performed. There have been virtually no surivivors among patients who have undergone pelvic exenteration with multiple positive pelvic wall nodes. Therefore, immediate frozen section analysis of the pelvic wall nodes is necessary in order to determine whether the resection should continue.

In Ketcham's[5] series of approximately 200 patients undergoing pelvic exenteration, only one who had a positive pelvic lymph node after irradiation therapy survived five years. In the series from Memorial Hospital for Cancer and Allied Diseases, New York City, reported by Barber,[6] 148 patients in whom radiation had failed had positive nodes at the time of exenteration, and only four of these patients survived five years. Most survivors with positive nodes had only microscopic disease in the nodes. Furthermore, in nearly every case reported in the literature of survivorship following exenteration for recurrent squamous cell carcinoma of the cervix in which there was a positive pelvic node, the nodal disease was not only microscopic but unilateral.

The pelvic lymphadenectomy having been completed, attention is turned to the status of the web or cardinal ligaments. The paravesical and pararectal spaces are developed and a critical assessment of the proximity of the central malignant disease to the pelvic wall is made. If there is a tumor-free space between the lesion and the pelvic wall, then resection probably is feasible. One must be cautious to analyze the entire web, especially the area immediately above the levator ani muscles. Often the most superior portion of the web will be free and then the surgeon will find dense adherence of the tumor to the pelvic wall inferiorly at the level of the levators. If removal of lymph nodes has shown no metastatic disease, it is at this point that the final decision is made as to whether or not exenteration is possible. Pelvic exenteration is not considered a satisfactory means of intentional palliation; the only established goal of this operation is complete cure.

Strenuous efforts have been made to decrease the permanent morbidity and increase patient acceptability of pelvic exenteration by tailoring the procedure to the known extent of the patient's disease. While it is rarely justifiable to salvage the bladder, because of its natural anatomic association with the cervix, the rectosigmoid flexure may occasionally be preserved and at times it is feasible to do a lower segmental resection of the rectum and then carry out re-anastamosis. A temporary diverting colostomy must always be done in conjunction with this maneuver. In most patients the possibility of constructing a vagina from a split thickness skin graft at the time of initial operation should also be considered. With these modifications, exenteration for pelvic malignant disease can frequently be performed, leaving the patient with but one stoma and a functional vagina.

Morbidity and Mortality

The morbidity and mortality directly related to exenteration occur within the first 18 months following the procedure. Many of the complications seen could be the sequel to any form of major operation. These include cardiopulmonary catas-

trophes such as pulmonary embolism, pulmonary edema, myocardial infarction, and cerebral vascular accidents. The length of these surgical procedures and the magnitude of blood loss definitely increase the incidence of cardiovascular complications. This category of complications usually occurs within the first week following the procedure. Then follows a period in which sepsis is the greatest threat to the patient's health and life. This sepsis usually has its origin in the pelvic cavity with the occurrence of a pelvic abscess or, more commonly, diffuse pelvic cellulitis.

One of the most serious complications following exenteration is small bowel obstruction related to the denuded pelvic floor. In the last decade several techniques have been utilized in an effort to avoid the adherence of small bowel to this large raw surface, including mobilization of omentum or abdominal wall peritoneum to cover the pelvic floor. When small bowel obstruction does occur, it is appropriately treated with conservative therapy. However, half of these patients come to re-operation and the mortality in this group approaches 50 percent. The risk of bowel obstruction is multiplied by pelvic infection and both conditions predispose to the development of small bowel fistulas, which always require re-operation and frequently augur a fatal outcome.

Complications in general are far more common in patients who have recurrence after irradiation therapy. Irradiated tissue is less likely to give good wound healing, and the formation of granulation tissue is severely retarded. The tendency for fistula formation is decidedly increased. Since surgical dissection after irradiation is usually more difficult, operating time and blood loss often are increased. Both of these factors are associated with higher morbidity and mortality. The long-term morbidity from exenteration centers mostly about complications related to urinary diversion. Once the period of susceptibility to sepsis has passed, urinary obstruction and infection become the major non-neoplastic life-threatening complications. Recurrent cancer is always the most likely long-term, life-threatening situation following the operative procedure, but the more preventable complications of the ileal conduit deserve primary attention. Long continued urinary antisepsis, perhaps for life, is advisable after exenteration. Pyelonephyritis is common and should be treated promptly and vigorously. Intravenous pyelography must be carried out periodically to assess the collecting system for hydronephrosis. A mild degree of obstruction is frequently retained following construction of an ileal conduit, but progressive hydronephrosis will require correction to salvage renal function. Death from remedial renal disease when there is no residual carcinoma is doubly tragic.

The morbidity and mortality from radical operation can be minimized by careful selection of patients; but the selection should not be so stringent as to deny resection in borderline cases for the outcome of recurrent carcinoma of the cervix without further treatment is clear.

Survival Results

The reported five-year cumulative survival after pelvic exenteration varies from 25 percent to 40 percent (Table 1). Reported survival rates depend on the circumstances of patient selection for exenteration. For example, where exenteration is a primary procedure the five-year survival rate is close to 50 percent. (Pelvic exenteration might be done as a primary procedure for carcinoma of the vulva extending up the vagina and into the rectum or bladder, and carcinoma of the cervix with extension into the bladder but not out to the pelvic sidewalls.) In contrast, the five-year survival associated with exenteration after full irradiation therapy for cervical carcinoma is much less than 50 percent in most series. Excluding the

TABLE 1.—
Reported Five-year Survival Rates after Pelvic Exenteration

Author	*Institution*	*Number of Patients Treated*	*Number of Operative Deaths*	*Number Surviving 5 Years*
KREIGER, J.[7] (1969)	Cleveland Clinics	35	4	13
BRICKER, E.[8] (1967)	Washington University	153	15	53
KETCHAM, A.S.[5] (1970)	NCI	162	12	62
SYMMONDS, R.[9] (1968)	Mayo Clinic	54	14	14
DOUGLAS, R.[10] (1957)	New York Hospital	23	1	5
PARSONS, L.[11] (1964)	Boston	112	24	24
RUTLEDGE, F.[12] (1965)	M. D. Anderson	108	18	31
BRUNSCHWIG, A.[13] (1965)	Memorial Hospital	535	86	108
TOTAL		1182	174 (15%)	310 (26%)

elderly, the obese, the heavily irradiated and other high risk patients would of course affect survival rates. Withholding exenteration if there is a positive pelvic node following pelvic irradiation also improves cumulative survival rates. In general, however, both the morbidity and mortality rates and the five-year survival rate have steadily improved over the last decade. Mortality rates in most centers are now well below 10 percent and morbidity rates are similarly lowered.

The outcome for many patients is related to certain preoperative findings. In the series from M. D. Anderson Hospital, 47 percent of the patients who had symptoms (pain or edema) with their recurrence but were found at operation to have resectable lesions, survived two years, whereas 73 percent of the patients who were symptom-free at the time of laparotomy survived two years. Of the patients who had a normal intravenous pyelogram at the time of laparotomy, 59 percent survived two years, while only 34 percent of the patients in whom the pyelogram showed some abnormality survived that long. In the group who had recurrence within two years of the primary treatment, 46 percent survived two years; if recurrence did not happen until five years or more after treatment, 61 percent survived two years. Therefore such factors as pyelographic findings, the presence or absence of symptoms and the interval between primary treatment and recurrence should be considered in the preoperative assessment of the patient, but here again they should not be so weighted as to forego the chance for cure in patients with resectable lesions.

In order for the mortality and morbidity to be acceptable, the operation should be done in medical centers by experienced surgical teams knowledgeable in the multi-disciplinary approach to cancer therapy who can tailor the management to each patient's needs. These ultra-radical procedures should be done only by surgeons with adequate training and background who are willing to take on the responsibility of long-term postoperative care and rehabilitation.

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Primary Venous Obstruction of the Upper Extremity

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Three cases of primary axillary and subclavian venous obstruction presented herein demonstrated the classic findings of swelling, aching or pain, and discoloration following effort in an otherwise healthy person. The clinical diagnosis was confirmed by venography. Residual changes were frequent after treatment that included anticoagulation and thrombectomy.

RECENT EMPHASIS on the study and treatment of vascular disease has been predominantly directed toward the arterial circulation; and when directed toward the venous side, the lower extremities have been the prime area of interest.[1] Primary venous obstruction usually occurs at the axillary[2] or subclavian veins as a result of thrombosis,[3-5] but may also be intermittent without thrombosis.[6-10] Secondary venous obstruction of the upper extremity is also well known, principally due to mediastinal compression or cardiac failure.[11-14]

Hughes reviewed the classic findings of venous obstruction of the upper extremity in 1949, and proposed that this entity following trauma in an otherwise healthy person be designated Paget-Schroeter syndrome.[11] Sir James Paget, in 1875, had published a lecture on "Gouty Phlebitis,"[15] and von Schrötter reported a similar case involving the arm of a healthy painter.[16] Many other names have been suggested, including "primary thrombosis,"[5,17-19] "traumatic thrombosis,"[20] "effort thrombosis,"[21,22] "effort phlebitis,"[23] "spontaneous thrombosis,"[7] "primary occlusion,"[24] "primary obstruction,"[25] and "primary deep venous thrombosis of the upper extremity."[26] Since many cases are not related to effort,[27] and thrombosis does not always occur, primary venous obstruction appears to be the most recently accepted designation.

The occurrence in a short period of time of several cases demonstrating the classic findings of upper extremity swelling, aching or pain, and discoloration, following effort in otherwise healthy persons,[28] who were then studied by venography (Figure 1), prompted this report.

CASE 1. A 33-year-old white woman had a history of swelling of the right upper extremity of five days' duration after playing baseball with her children. The right upper extremity was grossly swollen, 2 cm larger than the left. A venogram (Figure 2) revealed a segmental block approximately 2.5 cm long in the subclavian vein with excellent collateral filling through the thyrocervical trunk.

Therapeutic regimen consisted of elevation of the extremity and institution of anticoagulation with heparin. Anticoagulation with coumadin was continued for two months. At the time of discharge there was essentially no swelling nor limitation of motion involving the right upper extremity, and no subsequent problems developed during one year followup period.

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Figure 1.—Injection of antecubital vein with 30 ml of contrast demonstrated normal upper extremity veins with arm abducted.



Figure 2.—(Case 1) Demonstration of subclavian vein thrombosis beginning at the medial margin of the first rib and extending proximally 3 cm. This shows the "first rib bypass-collaterals."



Figure 3.—(Case 1) Venogram a year after Figure 2 shows recanalization of the subclavian vein and much less distinct first rib collaterals.



Figure 4.—(Case 2) Axillary venogram demonstrates propagation of the intravascular clot manifested by a clearly seen serpiginous filling defect.

A study one year later demonstrated that the occlusion had re-canalized, and the patient had no subsequent problems (Figure 3).

CASE 2. The patient was a 56-year-old man with a six-day history of progressive swelling and pain of the right upper extremity. The right upper extremity was grossly swollen and cyanotic. There were multiple dilated superficial veins over the right hemithorax. A venogram on the day of admission revealed a serpiginous filling defect involving the axillary and subclavian veins. There was extensive collateral circulation around the shoulder and neck (Figure 4).

The patient was treated with intravenous heparinization, elevation, and hot packs of the right upper extremity over a 24-hour period without improvement. On the following day, axillary venous thrombectomy was performed. Copious amounts of black, gel-like clot were removed via the axillary approach; however, it was not possible to reconstitute flow in this vessel. The patient was discharged with prescription of a therapeutic dose of coumadin. At that time, the right upper extremity had greatly improved and a Jobst right upper extremity garment was utilized. His subsequent course has been entirely benign, and at his last visit the patient had only minimal swelling of the right upper extremity and no motor or sensory deficit.

A venogram a year later showed a poorly recanalized subclavian vein and extensive collateral circulation about the right shoulder (Figure 5).

CASE 3. A 24-year-old man had fallen backwards with his shoulder abducted one week before admission. He noted a sharp tearing sensation in the right shoulder, and this was followed by pain and swelling in the shoulder and arm. On physical examination at the time of admission, swelling over the right pectoralis region, with tenderness to palpation, was noted. The superficial veins of the shoulder and right upper extremity were prominent. On elevation of the arm, there was delayed

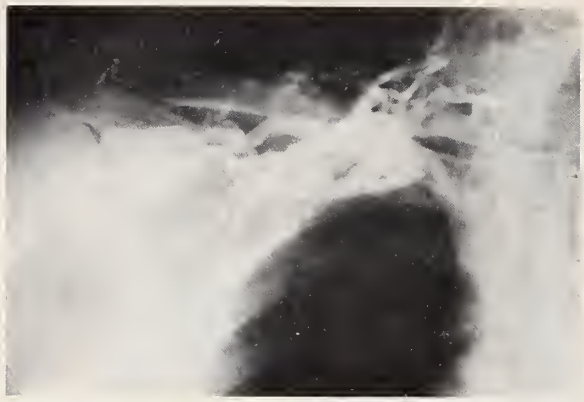


Figure 5.—(Case 2) Venogram a year after operation in Case 2 shows a poorly recanalized subclavian vein and extensive collateral vessels still demonstrated about the right shoulder.

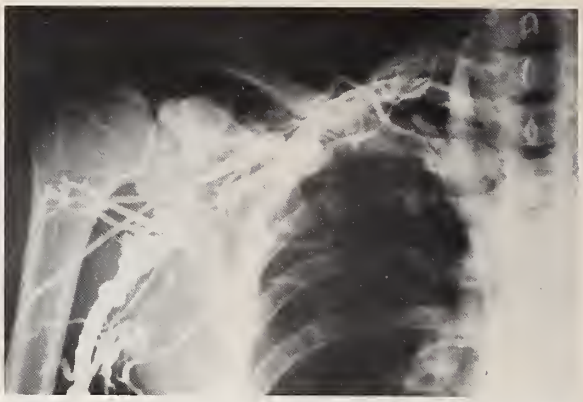


Figure 6.—(Case 3) Primary venous thrombosis beginning in the subclavian vein and propagation of the clot to involve the axillary vein.

emptying. The entire right upper extremity was considerably swollen. There was a bruit in the subclavian space and Adson's maneuver was positive.

A venogram on the day of admission revealed complete occlusion of the axillary and subclavian veins (Figure 6). An x-ray film of the chest showed no abnormality and no cervical rib. The admission diagnosis was effort thrombosis of the right axillary and subclavian veins, and scalenus anticus syndrome with partial subclavian artery obstruction. Scalenotomy was performed along with attempted venous thrombectomy. Anticoagulation was started in the immediate postoperative period with heparin. A large hematoma developed in the operative wound and the arm became progressively swollen. A second venogram showed complete block of the axillary and subclavian veins. Thrombectomy was done again. However, it was impossible to reconstitute flow in this vessel. At this time the middle third of the clavicle was excised as it was felt that this was contributory to the recurrence of thrombosis. Anticoagulants were not given during the postoperative period.

In a six-month period of observation after operation the patient improved considerably but had persistent swelling of the right upper extremity.

Discussion

Anatomy

The subclavian artery and vein leave the thorax arching over the first rib. The artery is posterior to the scalenus anticus and anterior to the scalenus medius, while the subclavian vein is anterior to the scalenus anticus muscle. They then pass together under the subclavius muscle and clavicle. The fascia in this area encloses the subclavius muscle and extends over the clavipectoral area. The lateral portion of this fascia is the costocoracoid membrane, which extends from the rib to the coracoid process. The vessels then enter the axilla beneath the pectoralis minor muscle and under the coracoid process, passing anterior to the humeral head.

The axillary vein is formed by the junction of the brachial and basilic veins at the lower border of the teres major muscle. The axillary vein joins the cephalic vein at the lateral border of the first rib, where it becomes the subclavian vein. After passing over the first rib, the subclavian vein joins with the internal jugular to form the innominate vein.[29]

A multitude of congenital factors have been implicated in vascular obstruction. These include cervical rib and bony protuberance on the first rib, bifid clavicle, failure of anterior curvature of the medial two-thirds of the clavicle, and hypertrophied subclavius muscle.[30,31] Abnormal insertion of the scalenus, the artery passing through the scalenus medius,[29] and anomalous transverse cervical artery compressing the vein,[7] and a prevenous accessory phrenic nerve[8] have all been described. Traumatic factors including clavicular fracture with excess callus[32] and subacromial dislocation of the humeral head have led to thrombosis, and iatrogenic factors including delivery, mastectomy, and operative procedures with the arm abducted have been implicated.[6] Also hypertrophy of the terminal valve of the axillary vein has been described.[9]

The principal dynamic factor leading to venous compression is the wide latitude of motion of the upper extremity, the scapulo-humeral joint showing the widest range of any joint in the body.[29] However, frequent arm motion results in a far lesser frequency of thrombosis as compared with

the lower extremity, estimates running anywhere from 2 to 10 percent.[26] The human thoracic cage is wide rather than deep as compared with the cage in animals and fetuses, and there is a low shoulder to thorax position as compared with children, especially in women. Either extreme of muscle tone can be involved with work hypertrophy, causing impingement on the vascular structures and loss of tone, resulting in sagging, especially in middle age.[29]

Symptoms and Findings

The presence of edema, usually non-pitting,[33] is the common denominator in almost all cases of venous obstruction.[11] In many articles primarily directed toward arterial obstruction, mention is made of clinical edema followed by the surgical observation of venous involvement as well.[29] The presenceof edema is usually measurable by increase in circumference of the upper extremity. Pain or aching and a cyanotic or reddish discoloration are usually present. Dilatation of the superficial veins in the deltopectoral region, best seen with infrared visualization, and increased venous pressure are usually observed.[28]

There may be mild paresthesias if only the vein is involved,[6] sometimes with numbness or weakness. Palpable venous cord[26] and tender axilla[21] are sometimes present.

Residual findings are the rule rather than the exception. They are noted in approximately 75 percent of cases. These include swelling, fatigue and discomfort, dilated veins, and shoulder or axillary pain.[21]

It is difficult to estimate the frequency of venous obstruction of the upper extremities, for many patients are not admitted to hospital, and in the majority of those who are the condition is not specifically diagnosed. Steinberg described 11 cases in 17 years[28] while four cases were observed at our institution in one year, but that frequency has not been subsequently maintained. Primary thrombosis is most common in boys and men 10 to 40 years of age, and the right side predominates in a two-to-one ratio.[11] The typical history is onset of symptoms within 24 hours after some unaccustomed "stress phenomena" such as lifting, playing baseball, or chopping wood.[21]

Pathogenesis and Course

The pathogenesis of neither the more common secondary obstruction on a cardiac basis nor that of stress thrombosis is well accepted. In severe cardiac disease, inadequate circulation is thought to lead to anoxia and resultant endothelial injury. This is complicated by increased blood volume, increased venous pressure, and capillary pooling.[12] In trauma,[34] the presence of edema results in impingement on the vein with slowing of the flow and resultant thrombosis. It is well documented that this is true thrombophlebitis, not a bland (loose) thrombus.[21] The thrombus is decidedly adherent so that embolization is rare,[22] there being only a few isolated references to pulmonary emboli from primary venous obstruction of the upper extremity.[1,22,35] Venous recanalization is rare,[34] so that reestablishment of adequate circulation is dependent on collateral vessels. If these are sparse, the prognosis is poor as far as residual clinical findings are concerned.[28] Gangrene is rare.[26,36] Mortality is virtually unreported.[11]

Diagnostic Maneuvers

There has been considerable confusion in regard to the various diagnostic maneuvers because of the variety of anatomic foci that may be involved, and to the not infrequent occurrence of positive maneuvers in patients who have no symptoms.[29] Various maneuvers may also produce bruits.

1. The *scalenus syndromes* are best demonstrated by the Adson maneuver and its variants. The scalene muscles function to raise the first rib, flex the cervical vertebrae, and unilaterally flex toward the side of contraction and turn the chin away. The Adson maneuver includes a deeply held breath, full extension of the neck, and turning the chin toward (or away from) the side being tested.

2. The *costoclavicular syndromes* are due to compression at the costoclavicular tract. These are produced by backward and downward thrusting of the shoulders such as occurs in soldiers with knapsacks, this resulting in narrowing between the clavicle and the first rib.[6,37] The costoclavicular space is bounded anteriorly by the inner third of the clavicle, the subclavius muscle from the outer clavicle to the first rib, and the costocoracoid ligament. The scalenus anticus muscle is the posterior boundary and the first rib the inferior. The subclavian vein is in the inner-medial angle of this space. The costoclavicular maneuver is an exaggerated military position, which frequently dampens the pulse in normal persons. A deep inspiration elevates the first rib, and elevation of the arm and thrusting the shoulders back and down results in backward rotation of the clavicle.[38]

3. *Hyperabduction syndrome* occurs during sleep and in certain persons whose occupations—painters and grease-pit mechanics for example—necessitate upward reaching. When the upper extremity is abducted to 180°, the vessels are at 90°, so there is a pulley effect across the pectoralis minor tendon, coracoid and humeral head. The clavicle extends upward and backward and the subclavius muscle and costocoracoid ligament are taut.[39]

Venography

In normal persons indentation of the subclavian vein as it passes over the first rib may be seen.[40] This is normally exaggerated when the arm is elevated.[28] Venous constriction is most often observed in one of three positions: (1) between the scalenus anticus and clavicle; (2) between the costocoracoid ligament and the subclavius and rib; and (3) in the axillary vein at the pectoralis minor[41] or subcapularis.[2]

Venograms are of value in demonstrating obstruction or thrombosis in the acute phase and persistent obstruction or recanalization later.[13] The demonstration of collateral vessels is of prognostic value. The "first rib by-pass collaterals" include the cephalic vein to transverse cervical to terminal subclavian or internal jugular veins, and the transverse scapular to the terminal subclavian vein.[26] Opinions on the necessity for venography differ, Hughes feeling that they are not of great value except for demonstration of collateral vessels.[11] Coon raises the possibility of danger due to irritation by the contrast media.[36] However, in certain instances such as hypertrophy of the terminal valve of the axillary vein, the study is diagnostic.[9] Some physicians utilize venography to determine indication for thrombectomy.[42]

Differential Diagnosis[26]

Cardiac failure is usually severe and obvious, frequently associated with hydrothorax, in patients with known rheumatic heart disease and mitral valvular involvement. Differential points include:[12]

Cardiac Thrombosis	*Effort Thrombosis*
pain, frequent and severe	not common
fever, slight	none
constitutional	none
left	right
arm and neck	arm only
female	male
middle age	young
embolism frequent[43]	rare[44]
prognosis poor	good

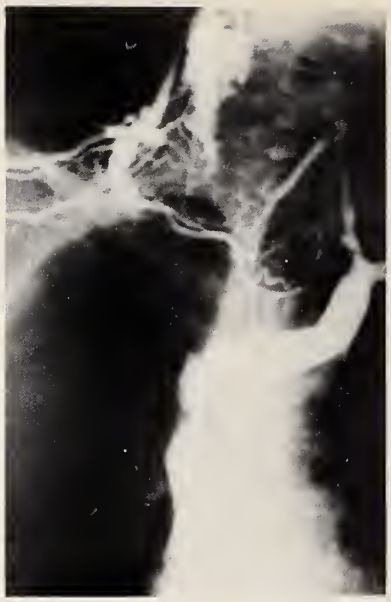


Figure 7.— Secondary venous thrombosis due to carcinoma of of the lung.

Mediastinal compression is most commonly due to neoplasm (Figure 7) resulting in compression of the innominate veins, especially the left. Substernal goiter and ascending aortic aneurysm may also exert pressure.[21] Axillary compression is usually due to metastatic carcinoma of the breast.[44]

Cellulitis and lymphangitis are not likely to be confused and neurologic involvement will include root findings, including those at the eighth cervical and first thoracic vertebral interspace.

The shoulder-hand syndrome, secondary to severe bursitis or coronary disease, leading to pain and immobilization with resultant atrophy and sympathetic nervous change, is characterized by cold, sweaty, and painful upper extremity, which becomes stiff, atrophic and fibrotic.[29]

Thrombophlebitis of the upper extremity in the past was usually secondary to intravenous medication, but recently is most commonly described due to sepsis with heroin or other illegal narcotics. Thrombophlebitis is also described with polycythemia vera, leukemia, pernicious anemia, and thromboangitis obliterans.[45]

Treatment

Anticoagulants are the principal agents of treatment.[26,36] They help alleviate symptoms, prevent propagation of the thrombus, and protect against embolization. There is, however, some opinion that they are not of value.[21,22]

Surgical operation has been advocated to remove the compression and enlarge the available space. Resection of the clavicle may be effective.[6] First rib resection, which is the preferred surgical

procedure for thoracic outlet syndrome,[46] has not been extensively utilized for primary venous obstruction. Anterior scalene tenotomy is not indicated for venous compression.[6] When the hyperabduction syndrome is present, pectoralis minor tenotomy may be of value.[47]

Operation usually has not been indicated for the acute thrombus since if there is a thrombus, there has probably been organization by the time the diagnosis is made,[48] and if there is not a thrombus, then collateral circulation should be adequate.[11] The high incidence of residual disability has recently led some observers to reconsider early thrombectomy.[13,33,42] Paravertebral sympathetic block and stellate ganglionectomy also have their advocates.[11] Ancillary measures include elevation of the upper extremity, compression bandages, and physical therapy.[9]

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Epidemiology of Viral Hepatitis in California, 1950-1970

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Epidemiologic patterns of type A (infectious) and type B (serum) hepatitis in California from 1950 to 1970 are presented. During this period hepatitis incidence increased greatly among teenagers and young adults but no significant increase occurred in other age groups. Much of this age-specific increase is related to the increasing drug abuse problem during the last decade. Other factors which possibly contribute to the current pattern of hepatitis in California are the overcrowding and inadequate sanitary facilities among a portion of young people between the ages of 15 and 30. Until these factors change or effective vaccines are developed, viral hepatitis will continue to be a significant public health problem.

VIRAL HEPATITIS IN CALIFORNIA is a public health problem whose importance has increased steadily over the last two decades. Between 1950 and 1970, there was, in addition to a pronounced increase in cases, a remarkable change epidemiologically in this disease. This report describes selected trends in the epidemiology of hepatitis in California during the last 21 years.

Material and Methods

In California, a system of reporting selected infectious or communicable diseases to the State Health Department has been in effect since 1913. Physicians are currently required to report over 50 illnesses to local health authorities, who in turn report these cases to the state. Viral hepatitis was not distinguished from other types of hepatitis as a single reportable disease until 1950. In 1955, a further distinction for reporting purposes was made between infectious (IH or type A) and serum (SH or type B) hepatitis. Starting in 1961, detailed histories were requested on all cases of hepatitis reported to the state. In 1968, the reporting procedures for hepatitis were modified further: a confidential morbidity report card which contains basic data such as name, address, age, sex, race, diagnosis and dates of onset and death continued to be required for both type A and type B but a detailed case history was requested only for cases of type B. Additional information obtained from the case history included details about hospitalization, blood transfusion, drug use, contact with other cases, tattooing, employment and the evaluation of the probable mode of contraction by the person completing the case history.

Diagnosis of either type A or B is made by the reporting physician; when a case is reported as hepatitis unspecified, it is counted as a case of type A. In general, physicians probably ask about a history within the preceding six months of (a) administration of blood or blood products, (b) self-injection of drugs, (c) tattooing, or (4) ear lobe puncture, to classify a case as type B. More recently, the presence of hepatitis-associated antigen (HAA) has been used to establish or confirm the diagnosis of type B.

It is recognized that gross under-reporting of hepatitis exists in the state. Yet no major changes

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in reporting procedures, with the exception of those described, have been made which would have significantly increased the level of reporting from physicians. Recognizing these limitations, we used the available data to describe selected trends in the epidemiology of hepatitis.

Findings

Case and Case Fatality Trends

Chart 1 presents cases and case fatality rates for type A (infectious) and type B (serum) hepatitis from 1950 through 1970. An upward trend with a superimposed seven-year cyclical pattern can be observed for type A cases: peak years occurred in 1954, 1961, and 1968. The chart shows that concurrent with the increasing number of type B cases, case fatality rate declined. In 1970 the fatality rate was only 1.1 per 100 cases compared with 14.8 per 100 cases recorded in 1951. Between 1960 and 1968 there was a continuous increase in reported type B cases which accelerated sharply in 1966. The type B case fatality rate also decreased considerably as the number of cases increased. Since 1968, cases of types A and B have dropped slightly but both appear, with minor fluctuations, to be stabilizing at a high level.

Seasonal Pattern

Data on hepatitis by month of report are available for the 21 years 1950-1970, and while this information is suggestive, it is not definitive because of varying delays from diagnosis to receipt of case reports. Information on month of onset is available for 1968, 1969 and 1970. No well defined seasonal pattern is apparent, but more cases of type A occur during the summer than at other times of the year. This slight seasonal elevation is most noticeable in the 1968 data. No seasonal pattern is noted for type B.

Age

The age distribution of type A cases during the peak years 1954, 1961 and 1968 is shown in Chart 2. The 1954 curve is typical of the age distribution observed in California before 1960: the highest case rate occurred in 5- to 9-year-olds. In 1961, the highest rate occurred in the 20- to 24-year group. In 1968, the rate found in the 5- to 9-year group was not significantly different from that recorded in 1954 and 1961, but clearly there is a huge increase of cases in 15- to 29-year-olds, with a peak in the 20- to 24-year group. For type B, almost no cases are reported in the under 15

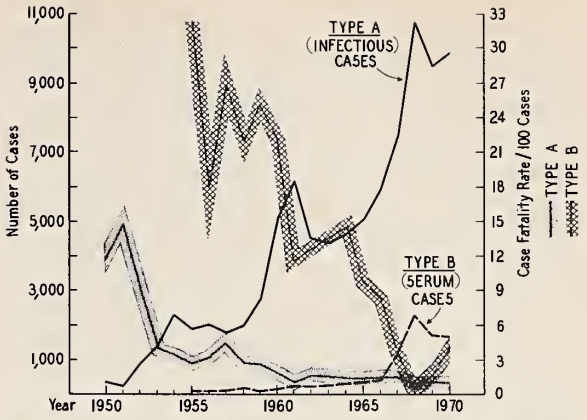


Chart 1.—Type A (infectious) and type B (serum) hepatitis, California, 1950-1970

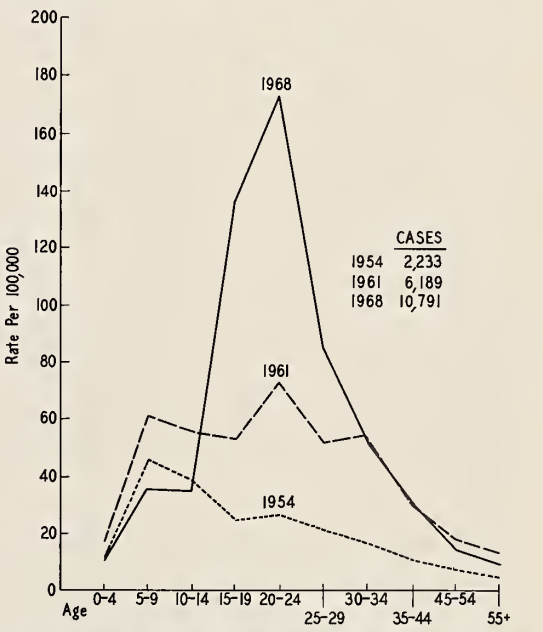


Chart 2.—Type A (infectious) hepatitis rates by age group, California, 1954, 1961 and 1968

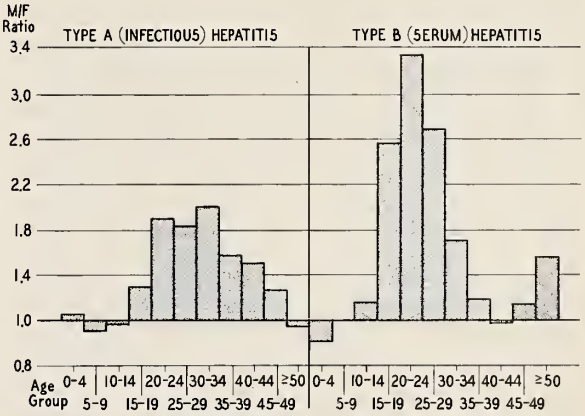


Chart 3.—Male-female ratio of viral hepatitis cases, California, 1963-1970

age group but the increase in incidence in the teen-age and young adult groups during the 1960's is even more pronounced than that observed with type A.

Sex

A preponderance in males is observed for both types A and B although the proportion of males is even greater for type B. Chart 3 shows that most of the sex difference during recent years is concentrated in the teen-age and young adult age group.

Geographic Location

The available data are not precise enough to allow detailed analysis of the geographic distribution of type A hepatitis cases in California. Until 1967 an effort was made to determine the county of probable contraction for hepatitis cases. In 1967 that procedure was changed and tabulations assigned each case to the county which first reported it. In most instances the county of report is the county of residence. An analysis of type B cases by county of report shows that this disease is at present concentrated in the high density population areas throughout the state. In 1961, type A rates were highest in the sparsely populated northern and eastern counties of the state, but in 1968 most of these counties had low rates compared with the more densely populated coastal counties.

Mode of Transmission of type B Hepatitis

Chart 4 shows an increase of parenteral drug use associated with type B which became very noticeable in 1966. In contrast, virtually no change is apparent in the amount of type B associated with use of blood or blood products.

Discussion

Traditionally, acute hepatitis of presumed viral cause has been classified as either infectious hepatitis (type A) or serum hepatitis (type B). Clinically, the types of hepatitis cannot be differentiated, but studies by Krugman et al[1] indicate that they are caused by different agents. The epidemiologic pattern for each type of hepatitis was considered to be distinct and consistent. Type A was said to have a short incubation period and considered to be predominantly a childhood illness transmitted from person to person via the fecal-oral route. Type B, on the other hand, was believed to have a long incubation period and to occur primarily in adults by transmission of the etiologic agent through parenteral inoculation of infectious material. Traditional definitions have not been substantiated by review of thousands of case records over many years. Furthermore, recent reports[1-3] indicate that type B may also be spread by the oral route and so even the established concept that modes of transmission differ for types A and B is no longer tenable.

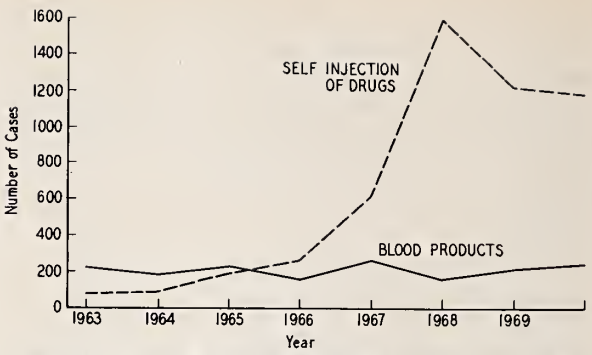


Chart 4.—Type B (serum) hepatitis cases associated with blood products or self injection of drugs

Over the last 21 years reported incidence of type A in California has increased in regular seven-year cycles. Gross under-reporting of overt hepatitis cases is known to exist and many mild and almost inapparent infections undoubtedly go undiagnosed. At present a conservative estimate of the annual number of hepatitis cases in California is 100,000. This estimate is based on reported cases, known under-reporting and the occurrence of inapparent infections. In addition to the sharp increase, other significant changes in occurrence of hepatitis are noticeable.

The current "epidemic" of hepatitis in California is confined to the 15- to 29-year segment of the population; no wide changes in hepatitis rates have been observed in other age groups. The decreasing case fatality ratio observed during the past two decades is probably related to this age shift, since fatal cases are rare among teen-agers and young adults. Similar trends in the distribution of hepatitis cases by age have been reported from New York[4] and New Jersey.[5] The preponderance of males, especially among needle-associated hepatitis cases, was also apparent in these studies.

The number of reported blood transfusion-associated hepatitis cases in California remained essentially unchanged during the past decade. One factor which may be partially responsible for this observation is that hepatitis rates have increased sharply only among teen-agers and young adults,

whereas the majority of blood donors are older adults. The stable number of transfusion-associated hepatitis cases may also reflect an increased tendency on the part of physicians not to report transfusion-associated hepatitis due to concern over medico-legal implications. Most likely both these factors plus closer screening of blood donors are responsible for this finding.

From review of recent studies on hepatitis,[6-8] it can be postulated that at least two etiologic agents for hepatitis exist. The distribution of these agents varies with geographic area and the living conditions of population groups involved. The incidence of hepatitis in childhood has not changed significantly in California during the last decade. The current age distribution with its peak among teen-agers and young adults appears to be a superimposition of a new pattern over that encountered before 1960. One study[9] reported that a large proportion of current "urban" hepatitis cases is probably type B. The geographic shift of hepatitis from rural to urban areas in California, the male preponderance and the virtual absence of a seasonal pattern may reflect the increasing prevalence of type B hepatitis.

The following is offered as a working hypothesis to account for the hepatitis pattern currently seen in California. If it is assumed that type A remains the predominant type of hepatitis in childhood, then most teen-agers and young adults may be considered to be susceptible to type B. The widespread self-injection of drugs[10] has established the etiologic agent of type B in this population group via the traditional parenteral route. Although type B transmitted via the fecal-oral route may not be as infectious as type A, the life style of this population segment can compensate for the assumed lower infectivity of the etiologic agent by conditions which promote spread of infection in many instances: relatively poor standards of personal hygiene, overcrowding and direct oral-genital contact.[11] Likewise, persons susceptible to type A because they did not contract it during childhood also stand a very high risk of acquiring it in this milieu. Most likely, these factors contribute to the very high rates and to instances of repeated episodes of hepatitis observed among some persons in this age group. Hepatitis incidence in California today thus appears to represent an increase in selected age-specific attack rates due to changes in the living conditions of a portion of the teen-age and young adult population. If so, current epidemiologic features of hepatitis vividly illustrate the profound changes in disease patterns which can be brought about by social change.

The development of laboratory tests for detection of hepatitis-associated antigen (HAA), which is believed to represent either the agent or an indicator of type B, will make possible further elucidation of the epidemiologic features of hepatitis. Blood banks throughout the state have made HAA testing a routine procedure. Hepatitis antigen-positive units of blood and plasma are discarded and the donors are permanently rejected. Also, an increasing number of laboratories offer HAA testing as part of the diagnostic test panel for viral hepatitis. Health Department viral hepatitis case report forms were revised in early 1972 to include data on HAA test results. Such information will provide a better understanding of the relative incidence of types A and B hepatitis in the population. Guidelines are being developed which describe the medical and public health management of those found to be HAA positive.[12]

The control of viral hepatitis continues to be an elusive goal since it can be achieved only by changes in the current living patterns among the population groups involved or the development of effective vaccines against both types of hepatitis. The likelihood of either occurring soon is remote, although results have been reported[13,14] which suggest the eventual development of vaccines to control this important public health problem.

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Changing Concepts of Prolactin in Man

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THAT THERE IS A HUMAN PROLACTIN, an entity separate and distinct from growth hormone, was until recently the firm conviction of the few. Progress has been so rapid that the year 1972 will almost surely be the last to see an authoritative publication appear in which doubt of the existence of human prolactin is either implied or expressed.[1] This article will summarize the important and rapidly accumulated evidence which justifies the statement that its existence is now a secure fact.

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In writing on "Changing concepts of control of human growth hormone secretion"[2] I avoided the problem of prolactin. Human growth hormone for more than a decade has been recognized to have unusually great prolactin activity when tested in the pigeon crop sac bioassay or especially in mammary gland bioassays.[3] To have discussed the control of growth hormone as a single molecule having a dual function, the second of which was the sole pituitary prolactin, I should have found impossibly difficult.

Controversy about growth hormone and prolactin is not at an end, and one of the points firmly believed by our group of investigators is that human prolactin behaves just as it should; human growth hormone, in contrast, is peculiar among

the growth hormones of mammals. It is this fact which slowed the recognition of human prolactin. A brief exegesis may be helpful.

A lot has been made of the structural resemblance of sheep prolactin to human growth hormone; electrophoretic similarities and even structural homologies have been stressed. This approach has not suffered from understatement. The facts are probably more accurately portrayed by stating that human prolactin is much like sheep prolactin;[4] indeed there is about 75 percent homology in the amino acid sequence of the two molecules according to this study. Most prolactins are more acidic than their corresponding growth hormones. Human growth hormone is peculiarly acidic, so much so that on disc electrophoresis it migrates ahead of human prolactin.[5] Human growth hormone is also peculiarly active as a lactogen. An epexegesis, for which I am indebted to Dr. U. J. Lewis, will follow, but the foregoing will orient the reader to a point of view.

Morphological Identification of Human Prolactin

The first essential for the identification of a new hormone is a willingness to concede its existence. Morphologists, to their great credit, were the first to exceed this minimal requirement; they pressed for the recognition of human prolactin, because they recognized a cell line with special staining characteristics. Three staining methods have been developed by which prolactin-secreting cells could be postulated. These are Herlant's tetrachrome, his methasol blue-PAS-orange G, and in 1968 Brook's stain.[6-8] Histological techniques suggested the presence of prolactin secretory granules in the tissue cultures of pituitary cells,[9] and in pregnancy pituitary cells were rich in these special staining cells.[10,11] Finally, special stains pointed to prolactin-secreting cells in certain pituitary tumors.[12] It is notable that the percentage of prolactin secreting cells in pregnancy reaches as high as 18 to 32.

Pasteels and colleagues,[13,14] convinced by the histological evidence, pursued prolactin production by human pituitary glands in culture. They amassed substantial data favoring production of a pituitary prolactin by cultures made from glands either of adult or of fetal origin. The cells with the staining characteristics implying prolactin production multiplied in the cultures; the proteins in the medium were rich in crop sac stimulating activity, and growth hormone secreting cells tended to drop out. Pasteels[15] showed that antiserum raised against human growth hormone did not neutralize the pigeon crop sac stimulating activity of the proteins secreted into the medium. Unfortunately the prolactin activity assayed only 2.95 IU per mg, about 10 percent the activity of a good sheep prolactin preparation. This was used as an antigen in one of the early radioimmunoassays attempted,[16] and some useful observations were possible with it. In my opinion, Pasteels more than any other investigator deserves to be credited with pioneering the identification of human prolactin.

Before leaving the histologic aspects, some remarks on pituitary cell nomenclature may prove useful, particularly for clinical consideration. Classifying pituitary tumors as acidophilic, basophilic, or chromophobic no longer fulfills the need for maximal accuracy. Nomenclature should relate more nearly to function. The established function of the anterior pituitary is to synthesize, store, and release six hormones. Separate cell lines secrete these hormones, and the goal should be a physiologically-based classification. Three hormones are glycoproteins, and these are thyrotropin (TSH), follicle stimulating hormone (FSH) and luteinizing hormone (LH or ICSH). The remaining three hormones contain no sugars, and their primary structure is that of a sequence of amino acids, 190 for human growth hormone and probably for prolactin, and 36 for corticotropin (ACTH). LH and TSH are each composed of two chains. Structural analysis has demonstrated that their B chains are identical, and this requires special precautions in radioimmunoassays. In the prolactins thus far studied there are six half-cystines, and these give rise to three disulfide bridges. Growth hormones have two disulfide bridges. Staining characteristics in modern work should be based on the affinities of the dyes for the specific hormones. These hormones under ordinary circumstances are present as secretory granules. However, when secretion is at a high rate little hormone is stored, and that cell line will be "degranulated." There appear to be resting cells in the pituitary gland, and they, too, will be poor in secretory granules. "Acidophils" are a combination of growth hormone, prolactin and ACTH secreting cells. "Basophils" generally contain glycoprotein hormonal granules, but intense cellular activity will be associated with sufficiently great numbers of ribosomes to give a basophilic reaction to the cytoplasm. "Chromo-

phobes" are a mixture of very active cells with few storage granules and of resting cells. Rarely are chromophobes truly undifferentiated cells. These considerations are pertinent, because it turns out that prolactin is probably the most commonly overproduced hormone in pituitary tumors.

Physiochemical Identification of Human Prolactin

The introduction of sensitive radioimmunoassays for human growth hormone made it possible to divorce galactorrhea in certain circumstances from growth hormone excess and even from measurable growth hormone in plasma. This implied the possibility of prolactin excess as cause of the breast secretion. Canfield and Bates[17] demonstrated stimulation of the pigeon crop sac by extracts made from the plasmas of five non-acromegalic patients with galactorrhea. Only one such extract was inactive. These observations, particularly when the extracts were made from blood of patients with pituitary tumors, implied that there was a separate prolactin. More direct evidence was supplied by Peake et al[18] when they found evidence of prolactin in a tumor removed from a patient with Forbes-Albright syndrome (galactorrhea and amenorrhea with or without pituitary tumor). The positive crop sac response, in contrast to that to human growth hormone, was not prevented by previous incubation with antiserum raised against human growth hormone. Further, using the disc electrophoretic method developed for studying growth hormone and prolactin in rats by Jones et al,[19] they demonstrated a major band moving more slowly than growth hormone. They clearly recognized they had not shown this to be the prolactin band and commented that the relative mobilities were unusual. These authors also cited, in support of the idea of a pituitary prolactin separate from growth hormone, the studies of Ehni and Eckles and those of Field et al.[20,21] These were neurosurgical reports that pituitary stalk section resulted in galactorrhea despite diminution of growth hormone secretion.

The foregoing reports were highly suggestive of a separate human prolactin, but they were all made in abnormal situations and open to another interpretation by those devoted to the unified growth hormone-prolactin theory. The counter argument could run to the effect that in disease only the prolactin moiety of the molecule was made.

In our laboratories the strong interest of Lewis had not only led to involvement in evolutionary aspects of structure and function of growth hormones and prolactins but also to conviction that the new clues in man pointed to a separate prolactin. Our earlier studies with Jones[19] centered our interest on obtaining pituitary glands from patients who had been receiving (or making) estrogens at the time of death; for we had found with disc electrophoresis that the "prolactin band" of the pituitary was much larger in mature female rats than in males and that this was an estrogen effect. Through the kind helpfulness of Dr. Averill Liebow and his staff at University Hospital, San Diego, we were provided with the opportunity to study postmortem the pituitary of a woman who had been taking estrogen and that of one who had died just after the termination of pregnancy. From these glands it was possible to isolate the protein of a molecular weight of 20,000 Daltons, a prolactin activity of at least 15 I.U. per mg, and to demonstrate a new constituent of the normal pituitary, a protein band moving on disc electrophoresis just behind human growth hormone.[5] More important, this study provided a marker in disc electrophoresis for following prolactin in the extraction of large batches of frozen human pituitary glands. These were kindly supplied by the National Pituitary Agency and enabled Dr. U. J. Lewis and his group to extract human prolactin in highly purified form for further identification and for structural studies.[4,22]

At the same time, Friesen and his colleagues in Montreal were making an excellent series of important advances in the areas of monkey and human prolactins. Their studies are summarized in a chapter of Human Lactogens,[23] but unfortunately this volume is not widely available. A brief account of these crucial studies will be attempted. Friesen and his group cultured pituitary glands of monkeys, normal human pituitary glands obtained at operation for breast cancer, glands from acromegalic patients and from patients with galactorrhea. These pituitary fragments in culture secreted proteins into the media. Radioactive leucine, introduced into the culture fluid, was incorporated into the proteins and served to label them. The remarkable finding was that gel filtration of the media not only resulted in a single large radioactive peak but also that an antibody raised against human placental lactogen or growth hormone precipitated much less of this material than did antibody to sheep prolactin. This supported their inference that

the human pituitary gland, like that of animals, secreted prolactin and that there was some structural similarity of this human hormone to sheep prolactin.[24,25] Tumors from patients with galactorrhea were found to secrete into the medium preponderantly prolactin, whereas glands from acromegalic patients tended to secrete much more growth hormone. For purification studies the technique of affinity chromatography was then pursued. In this procedure antibody is coupled to Sepharose; when the labeled protein mixture was passed over the column, labeled prolactin or labeled growth hormone was bound according to which antibody had been coupled to the Sepharose. They were clearly able to prepare human prolactin in small quantities but of good activity (13 I.U. per mg) and with very little contamination. In 1972, they presented their method for preparing human prolactin of high activity from a side fraction of the Raben procedure for making human growth hormone.[26] This preparation and that of Lewis gave virtually identical inhibition when tested by their radioimmunoassay.[27]

Biochemistry of Human Prolactin

The first published methods for the extraction of human prolactin were those of Lewis et al[4,22] and of Hwang et al.[26] In the Lewis procedure the starting material was frozen human pituitary glands. The final product was about 5 micrograms of prolactin per gland. Its potency in the pigeon crop sac assay was about 30 I.U. per mg, comparable to sheep prolactin potency of the National Institutes of Health (NIH) standard. Success required a means of following the prolactin component through the extraction procedure, and this was made possible by the findings on disc electrophoresis already noted. A second requirement was mastering problems of hormonal instability during extraction. This is a trying problem because of the low concentrations of prolactin in the starting material. Glands stored frozen clearly lose their prolactin. A perhaps more intriguing problem is that human growth hormone undergoes specific cleavage during storage and extraction, and this cleavage is attended by enhanced prolactin activity in crop sac assays. The cleavage does not, however, lessen growth hormone activity by tibial test or by radioimmunoassay. This enhancement of prolactin effect by this means is peculiar to human growth hormone.

The method now in use[4] goes back to the original ethanolic extraction procedure by which Bates and Riddle first isolated sheep prolactin in 1935. Freeing the partially purified prolactin of contamination with growth hormone can be accomplished chromatographically by a variety of techniques, including diethylaminoethyl (DEAE) cellulose and carboxy methylcellulose. The preparative method of Hwang et al, using the Raben extraction by-product, appears to yield a highly suitable human prolactin.[26]

The primary structure of human prolactin, that is, in terms of its amino acid sequence, has already been approached by two methods. Lewis et al,[4] using the method of tryptic digestion and amino acid analysis of the peptides isolated on two-dimensional paper chromato-electrophoretic separation (finger-printing), have proposed about 80 percent of the human prolactin structure. They found a molecular weight of 20,000 Daltons, a leucine amino terminus, three disulfide bridges, and about 75 percent homology with ovine prolactin. This type of sequence prediction depended on the known structure for ovine prolactin.[28] At the same time Niall,[29] in collaboration with Friesen, analyzed the amino terminal portion of the molecule, using the methods of Edman degradation, cyanogen bromide and tryptic cleavage. This exacting procedure, which consumes much more prolactin, is in such good agreement with the finger-printing method that it appears highly probable the estimate of 70 to 80 percent homology between human and ovine prolactins will prove to be fully justified.

The evidence to date speaks for the similarities in the structures of prolactins of human, ovine and bovine origins. If closer similarities between mammalian prolactins than growth hormones turn out to be the general rule when more structure data are at hand, there will already be an exception. Thus, rat and mouse prolactins almost surely have far less structural resemblance than the corresponding growth hormones. The most remarkable aspect of structure-to-function relationship is that which exists between human placental lactogen and human growth hormone.[30] The former is primarily lactogenic and a weak growth hormone. It does little or nothing to potentiate the growth effects of growth hormone. However, there is a pronounced similarity of the structures of these two hormones, evidence which probably should be taken to testify to the uniqueness of human growth hormone.

Measurement of Human Prolactin

Homologous radioimmunoassays for human prolactin are now available.[31,32] We have supplied materials for this assay to the National Pituitary Agency for distribution for research purposes. There can be little doubt that this method will be one of choice for the measurement of prolactin in blood and other body fluids. Nonetheless, very important advances in the understanding of prolactin secretion in health and disease were made with ingenious bioassay procedures of surprising sensitivity; none measured prolactin in the concentrations found in normal human blood. Kleinberg and Frantz[33] devised an assay based on histological evidence of milk production by the cultures of mammary tissue taken from mice two weeks pregnant. Prolactin in plasma of women could be detected by this assay, and elevations induced by lactation, by drugs, and in abnormal states were clearly defined. Human growth hormone also stimulated the mammary tissue, but this difficulty was obviated by neutralizing the growth hormone in plasma by addition of specific antibody. Loewenstein et al[34] devised an assay based on activation of a synthetase for n-acetyllactoseamine, and Turkington[35] found mammary tissue sufficiently sensitive to prolactin that incorporation of[32] phosphorus into milk proteins provided a suitable bioassay system. In England, Forsyth used a rabbit mammary gland culture system, capable of measuring prolactin in blood of mothers after suckling and of some patients with non-puerperal lactation. A scholarly article by Forsyth and Edwards[36] has just appeared, reviewing the field and the numerous contributions of these workers.

Heterologous radioimmunoassays are capable of measuring prolactin in human blood.[37] Here the structural similarity of ovine to human prolactin is often the essential factor. As in homologous assays, antibody is raised in rabbits, but in this case ovine prolactin is used as the antigen. The antibody so raised has been most successfully employed to bind radioiodinated porcine prolactin.[38] Inhibition of this binding was found with a human plasma rich in prolactin, enabling a standard curve to be constructed. In another heterologous assay Friesen et al[27] induced antibody in rabbits against monkey prolactin and iodinated sheep prolactin. When they substituted primate prolactin for iodination, the result was a great increase in the sensitivity of their assay.

Because it gives an intimation of structural differences in terms of immunoreactive sites, special interest attaches to the cross-reaction of the prolactins of lower species in the homologous human radioimmunoassay for prolactin. The question here is what prolactins of lower species have sufficient similarity to human prolactin to inhibit the binding of the labeled human prolactin to an antibody raised against it in rabbits. In our totally homologous system, ovine and bovine prolactins inhibited binding of human prolactin to its antibody to a considerable extent. In the jargon of the field, the curves of inhibition were not parallel, suggesting that these prolactins were sufficiently different structurally in the critical areas that affinities between them and the antibody differed from that for the human hormone. Mouse prolactin in the radioimmunoassay gave a weaker nonparallel inhibition, and rat, pig, whale, turtle, frog and shark prolactins did not cross-react at all. Interestingly and in agreement with Friesen's Montreal group, we found no inhibition by human placental lactogen. Also in agreement with them, we found human growth hormone to cross-react only at very high concentration and interpreted this to be a measure of the degree to which human growth hormone was contaminated by human prolactin.

In practical terms, these studies mean that human prolactin can be measured accurately in blood despite maximal levels of growth hormone, such as are found in acromegaly. Further, human placental lactogen offers no obstacle to the measurement of human prolactin at any point in pregnancy. This is in contrast to the situation which is found with growth hormone which cannot be measured with any ease in pregnancy because of the cross reactions between it and human placental lactogen. Again this reflects the peculiarity of human growth hormone, its structural similarity to a lactogen and its own innate lactogenic activity.

One other point deserves elaboration. Despite the failure of pig prolactin to inhibit binding of human prolactin by the latter's specific antibody, pig prolactin can be used for radioiodination in the heterologous assay, as mentioned. Binding of this pig prolactin to antibody raised against sheep prolactin is inhibited by human prolactin. Since both pig and sheep prolactins have been available for years, the necessary ingredients for a sensitive heterologous assay have been on hand for a considerable time, substantially longer than there has been agreement on the existence of human prolactin as an entity.

Physiology of Human Prolactin

Blood drawn from ambulatory adults, men and women, contains on the average about 10 nanograms prolactin per ml. The range is not defined. The influences of age, sex, time of day, relation to meals and to sleep have not yet been fully explored. Friesen[39] reports the newborn to have pronounced elevations of prolactin at birth and continuing for a week (200 ng per ml falling to 50). The functional significance of this is as obscure as it is intriguing. Men, in whom the function of prolactin is almost entirely to be worked out, have about the same blood concentrations of prolactin as women. The luteal phase of the menstrual cycle may be marked by a slight rise in mean prolactin levels; if so, it appears not to exceed a 10 percent rise.

Sassin et al[40] and L'Hermite et al[41] have reported nychthemeral changes in secretion of prolactin. There is a sleep release of prolactin, but much remains to be investigated concerning its nature. Parker and Rossman[42] have found that daytime naps are associated with rises in prolactin concentrations in blood. They found with frequent bleeding that there is a broad swing in these values in around-the-clock studies, indicating the need for caution in assigning normal values and even in evaluating stressful and pharmacological influences.

Pregnancy is associated normally with a progressive rise in plasma concentration of prolactin. A fair rule of thumb for the present is that prolactin concentrations double in the first trimester and again in each subsequent trimester, finally rising at term to about 200 ng per ml.[39]

The nursing mother when not being suckled has a 10- or 20-fold elevation of concentration of prolactin in blood during the early part of the puerperium. There is a sharp rise with the suckling stimulus so that the concentration of prolactin is further doubled for some 30 minutes. As time progresses, the basal elevations and the responses to suckling are less in magnitude but each appears to be measurable over several months.

A somewhat surprising stimulus to the secretion of prolactin is the thyrotropin releasing factor or hormone (TRH). The rise is prompt, often maximal in 15 to 30 minutes after intravenous doses of TRH as low as 10 mcg. In clinical testing 200 to 500 mcg of TRH is commonly employed. Rises to 50 ng per ml and substantially higher are common. Interestingly, as with thyrotropin, prolactin is released by TRH to greater heights and for a longer time in hypothyroidism.[43,44] TRH has reduced effectiveness in releasing both prolactin and thyrotropin in Graves' disease. Physiological significance for the release of prolactin by TRH cannot be claimed. It is notable, however, that galactorrhea occurs in an occasional patient with hypothyroidism.

In lower animals prolactin secretion is generally held to be unique among the pituitary hormones. Prolactin, it is held, is released by the pituitary gland unless the release is prevented by the hypothalamus through its "prolactin-inhibiting-factor." There is support for this concept, including evidence from man. Ectopic location of the anterior pituitary or section of the pituitary stalk appears to release the prolactin secreting cells from the tonic inhibition of the hypothalamus. Stalk section certainly appears to have this effect in man.[45]

The full account of control of human prolactin secretion remains to be worked out, but it seems clear that the catecholamines are important in the pathway of release. One use of the TRH studies of prolactin release is to enable a reasonable calculation of the disappearance rate of prolactin from plasma. In studies we have done in collaboration with Dr. Inder Chopra of the University of California, Los Angeles, Department of Medicine, it repeatedly appeared that in 15 minutes prolactin concentration declines its peak to a concentration 50 percent or more below the peak. We have seen a half-time of less than 10 minutes in this type of study with TRH. This is in keeping with figures stated by others for the disappearance rate of this hormone from blood. The rapidity of disappearance suggests that the effect of TRH on the prolactin secreting cells is of very brief duration.

A physiological role for prolactin in lactation is beyond doubt. The nature of the receptor proteins of mammary tissue and the translation of the hormonal stimulus to enzymic action is already unfolding; Turkington and his colleagues have recently summarized their many contributions on this topic.[46] That lactation has been essential to the long term survival of man would seem beyond reasonable doubt and a sufficient reason for there being a prolactin. The role of the prolactin in such high concentration in the newborn and the presence of the hormone in the male pose solid unanswered problems. Fascinating suggestions in consideration of these roles are found in lower forms. The euryhaline fishes require an intact pituitary for maintenance of salt and water balance in going from sea water to fresh water,

and prolactin restores the defect that hypophysectomy induces in this balance. It appears that hens bred for egg-laying capacity have had prolactin bred out of them, and cows bred for milk production have high concentrations of prolactin. The former are broody under the influence of prolactin; the latter, especially the prize milk producers, are susceptible to a bizarre behavioral disorder which is accompanied by failure of lactation.[47] Here the role of prolactin is uncertain. In some rodents prolactin is luteotrophic and essential for the maintenance of pregnancy, a role not played by this hormone in human beings. Prolactin is "antigonadal" in some respects, and this may be a significant function for human prolactin. Nursing mothers are so protected against conception that subsequent pregnancies are delayed nearly one year without contraceptive measures. The method is not fully reliable.

In the male newt prolactin augments the effect of testosterone on the nuptial pad, a device for clasping the female during amplexus. In the male mouse prolactin plays a role in fertility. In the male rat prolactin enhances the effect of testosterone on the prostate, and induction of binding sites for testosterone has been described in the human prostate.

Another line of evidence of nonlactational effects of prolactin is found in the studies of ovine prolactin in man. The abundance of ovine prolactin, its rather superficial resemblances to human growth hormone and the scarcity of the latter, clearly prompted this type of study. Although this bias slanted the selection of the physiological effects to be observed, the newer evidence of a strong homology between the prolactins of man and sheep suggests that the effects observed after injection of sheep prolactin be regarded primarily as clues to the mode of action of human prolactin. One difficulty with the acceptance of this approach is that the ovine prolactin was injected in individuals without knowledge of their endogenous prolactin concentration, but this reservation would apply chiefly where no responses were noted. Further, the homology is incomplete, and the studies therefore provide clues rather than proofs. For these and some additional reasons, quantitative comparisons of human growth hormone effects and ovine prolactin effects probably should not be made.

If we accept the hypopituitary and the hypophysectomized patients as most suitable for these studies, the following effects have been found with reasonable frequency after ovine prolactin: fall in blood urea nitrogen, increased urinary calcium and phosphorus excretion, glucose intolerance, and occasional increase in sodium excretion. In balance studies nitrogen balance has tended to be positive.[48] Nitrogen retention has also been observed regularly in the few cases treated with bovine prolactin, and interestingly in view of what has been said about structure, pig prolactin has caused decidedly negative nitrogen balance.[49] Although in our laboratory the yields of human prolactin have been improving substantially with better storage and extraction methods, we see little hope for human prolactin's being available in the requisite amount for metabolic studies in the near future. Pharmacological and clinical clues to the mode of action of prolactin in man and the use of homologous prolactin in animals should, however, provide new evidence of the physiological role of prolactin.

Pharmacology of Human Prolactin Secretion

Fairly extensive studies in the rat, well-known to have high concentrations of hypothalamic catecholamines when compared with the brain generally, show that depletion of hypothalamic catecholamines by drugs results in elevation of blood prolactin content. This appears to occur because of a reduction in prolactin-inhibiting factor. Further, drugs which elevate the catecholamine content of the hypothalamus lower blood prolactin levels. For many years it has been observed that psychotropic drugs, such as chlorpromazine, result in galactorrhea. The frequency with which milk appears in the breast varies with the configuration of the drug, dosage and duration of administration. Apostolakis et al have recently recorded an extensive experience with these drugs, used singly and in combination, for their effects in producing galactorrhea.[50] These drugs deplete the hypothalamus of catecholamines, and the effect of chlorpromazine can be used to test for prolactin secretory capacity of the pituitary gland.[51] In this test 25 or 50 mg of chlorpromazine injected intramuscularly results, in one to two hours, in 10- to 20-fold rises in the blood concentration of prolactin. Chlorpromazine causes hypotension and should be used cautiously for this purpose. As mentioned above, TRH also releases prolactin. This effect is of unknown physiological significance, but the apparent lack of side-reaction to this tripeptide may make it valuable as a drug in testing for prolactin release. Reserpine, alpha-methyl-*p*-tyro-

sine, methyl dopa, and d-amphetamine are among the agents which deplete catecholamines. Their place is not yet determined as pharmacological agents for the study of pituitary reserve. Reserpine as a galactorrheic agent which enhances prolactin secretion is clearly recognized.

In the studies of Turkington,[52] L-tryptophan given in 10-gram dosage over 20 minutes intravenously causes a prompt, many-fold release of prolactin. Presumably this action depends on the formation of hydroxytryptophan and possibly serotonin. In contrast to tryptophan, L-dopa suppresses prolactin secretion in man, and this pharmacological effect of levodopa has been used both in testing and in treatment.[27,38,53] Dosage has ranged from 250 mg three times a day to 500 mg four times a day. Prompt cessation of lactation with prolonged effectiveness of the medication and with resumption of menses in some instances has been observed. It is probable that the effect of L-dopa is on the hypothalamus to promote the release of the prolactin-inhibiting factor. Since dopamine may be a releasor of the gonadotropins, the resumption of menses may not depend on the suppression of prolactin but rather represent a direct effect of catecholamines on the luteinizing hormone releasing factor. In my opinion, this remarkable effect of L-dopa raises the possibility that the hypothalamus, normally rich in catecholamines, may be subject to a disorder of biogenic amine metabolism, with multiple or variable manifestations. This would be rather imperfectly analogous to the thalamic disorder in paralysis agitans.

A good deal of interest exists in synthesizing derivatives of ergot as suppressors of prolactin secretion. This effect has been documented in rats, and a very preliminary report[54] indicates some success in galactorrhea with a brominated ergocryptine. Prolactin excess was not demonstrated, however, and the drug was not well-tolerated in this limited experience. Forsyth et al[36] have had favorable experiences with ergot derivatives for suppressing prolactin secretion. Action here is said to be directly on the pituitary gland.

Clinical Significance of Prolactin

Although so much remains to be explored, it is already clear that the measurement of prolactin in the body fluids of man will not only be of great physiological interest but also of great clinical import. Hypersecretion of prolactin as the most common abnormality in pituitary tumors seems almost certainly to be beyond dispute. Friesen, for example, with his colleagues[39] states that it is mandatory to measure prolactin in all pituitary tumor patients. In support of this contention, he cites evidence that whereas growth hormone hypersecretion characterizes 15 to 20 percent of pituitary tumor the figure is about 30 percent for prolactin. In our studies[32] the incidence of elevated prolactin secretion in acromegaly is higher than in Friesen's experience, so that he may have underestimated the frequency with which prolactin hypersecretion occurs in patients with pituitary tumors. The more important point is that prolactin hypersecretion in his study occurred with pituitary tumor frequently when there was no inappropriate lactation. Indeed, only one third of the patients with pituitary tumor and elevation of plasma prolactin had galactorrhea.

It must be acknowledged, however, that pituitary tumor is of fairly infrequent occurrence and that galactorrhea as inappropriate lactation is arbitrarily defined and of uncertain incidence. It appears not to be known at what point after the cessation of nursing expressible secretion should disappear. Indeed the fact, as presented by Daughaday's group at the Fourth International Congress of Endocrinology, that the male responds to nipple stimulation by his wife with distinct elevation of plasma concentration of prolactin suggests that continuing induction of specific protein kinases in the human female breast in response to prolactin may better be considered in terms of sexual behavior than too readily regarded as pathological. The larger questions involve the role of prolactin in disease. In the mouse, virus induced mammary cancer and, in the rat, chemically induced mammary cancer have been shown to be prolactin-dependent. It is already apparent that human breast cancer, however, is not characterized by elevation of plasma prolactin concentrations as determined in randomly drawn samples. This statement by no means should be taken to exclude prolactin from a role. The complexity of the problem is indicated by the number of hormones that act on the breast—insulin, cortisol, thyroid hormones, prolactin, growth hormone, placental lactogen, estrogens, and progesterone. Forsyth and Edwards in their comprehensive essay on human prolactin[36] have made an extension to this point of the studies of Meir et al,[55] who showed that whether prolactin induces crop sac responses or lipogenesis in the pigeon depends on a phasic relationship to corticosterone. Eighteen hours after corticosterone injection, prolactin induces crop

sac responses: six hours later it promotes lipogenesis in liver and gut. With so many pituitary hormones showing normal, independent rhythms, with diurnal variation in responsiveness to insulin, and with the cyclic nature of the female gonadal steroid secretion, it is apparent that the endocrinology of mammary tumorigenesis may pose most complex problems. In addition, if the mouse disorder is a model for the human disease, the virus may complicate the problem, even in terms of its endocrinology. We have developed mouse growth hormone and prolactin radioimmunoassays[56,57] to pursue the study of the mouse as a model for breast cancer. It is already clear that the pituitary and blood concentrations of these hormones differ between the C_3H/St strain which transmits the tumor virus in the milk and the C_{57}BL strain which is tumor-free and does not transmit the mammary tumor virus in the milk. Further, the switching of litters to nursing dams of the opposite strain is followed by significant changes in the pituitary concentrations of these hormones. Genetic and nutritional factors, as well as the virus, may have roles in these experiments. Clinical underscoring of the complexity of the problem comes from two apparently contradictory observations. L-dopa is thought to have had some beneficial effects on metastatic breast cancer, presumably through prolactin suppression. Stalk section, releasing the pituitary from the influence of prolactin-inhibiting factor and favoring prolactin secretion, has also been found beneficial. In addition, hypophysectomy which should lessen or abolish pituitary secretions has had significant beneficial effects in metastatic breast cancer. The contradictions may be only apparent, for the rhythms characterizing secretion of the involved hormones will be altered by these maneuvers. As stated in the earlier review,[2] patients with breast cancer have paradoxical releases of growth hormone in response to glucose loading, which also suppresses corticotropin. The full consequences of such a disruption of the normal secretory pattern are at present unknown. It would seem biologically important that in man growth hormone is secreted in the early hours of sleep, prolactin and thyrotropin later in sleep and in the early waking hours. Meantime, plasma cortisol concentrations are minimal during the time when growth hormone is actively being secreted, and plasma cortisol is at about maximum when the prolactin and thyrotropin are at peak concentrations. Sometime later the thyroid will have responded to thyrotropin by secreting thyroid hormones. Quite apart from the remaining hormonal influences on the breast, it seems reasonable to expect that disrupting the sequence may play both pathogenetic and therapeutic roles.

Whereas the breast remains a focus of medical interest in the role of prolactin in health and disease, we may only ask questions about other structures on which prolactin may have important physiological or pathological bearing. As a hormone that affects behavior in animals, is it related to mood in man? Is its sodium retaining activity of major significance in certain pathological states? Why is it in high concentration in the blood of the newborn—and in amniotic fluid? Does it play an unexpected role in much of amenorrhea? Does it have a relationship to diabetes? What does it do in men? The past two years have been exciting for those interested in endocrinology; the next two years should see better questions asked. Better answers, too.

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Refer to: Malaria—Medical Staff Conference, University of California, San Francisco. Calif Med 118:38-45, Feb 1973

MEDICAL STAFF CONFERENCE

Malaria

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* *Malaria is a disease of worldwide importance, but one which we infrequently encounter here. Dr. Robert Dreisin will present the case of a patient who was treated here.*

DR. DREISIN:† The patient is a 21-year-old Nicaraguan woman who was presented to us with a history of two weeks of chills and fever. She was apparently well when she left Nicaragua for the United States four months before admission. Two weeks before admission she noted a mild chill with fever, which lasted about four hours, then faded. It occurred the next day and approximately two days thereafter. The attacks were of increasing severity and she noted scleral icterus and darkening of her urine with the attacks. By the time she was presented to us in the Emergency Room she had been treated by a wide variety of physicians with a wide variety of antibiotics. On physical examination the patient was in no acute distress and was afebrile. Mild scleral icterus and a hemic cardiac flow murmur were present, but results of the physical examination were otherwise unremarkable. There was no hepatosplenomegaly. Admission hematocrit on the blood smear revealed many Plasmodium vivax ring forms (trophozoites) and larger red blood cells, with schizonts present. There were some merozoites but no gametocytes on the smear. The patient was treated with chloroquine and she remained afebrile and asymptomatic thereafter.

DR. SMITH: *She has been seen in the clinic for subsequent followups and is doing well. She is not actually here for presentation this morning. Our discussant will be Dr. Donald Heyneman, Professor of Parasitology in the Department of International Health.*

DR. HEYNEMAN:* The present case is very typical of uncomplicated vivax malaria. The patient is one of about 200 million persons who suffer from malaria annually, that is equal to about 12 percent of the 1.7 billion humans—half the world's population—who occupy various tropical and subtropical regions of the world that are or recently were endemic for malaria. About 650 million people, 38 percent of the exposed population, are now considered freed of malaria and another 710 mil-

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lion are partially protected or freed of endemic (but not of periodic) malaria. Yet there are still 380 million more, chiefly in tropical Africa and the Amazon basin, where no malaria control has begun.[1] It has been roughly estimated that about half of these unprotected people are infected. Concern in this country has been greatly heightened by the reappearance of imported malaria in the United States, chiefly from returning Vietnam veterans—4,000 cases in 1970, 3,000 in 1971. The whole question of malaria is now in a confused state due to importation and reappearance of malaria in areas in which it was thought to be controlled (or even eradicated), the development of widespread resistance to insecticides by the mosquito vectors, and in Southeast Asia and South America the resistance of the most dangerous plasmodial agent to drugs.

There have also been political or administrative interference and financial slowdowns of many malaria eradication campaigns, leading to loss of the World Health Organization (WHO) thrust and of public confidence in the possibility of worldwide malaria eradication, a basic WHO goal since 1955. This campaign is one in which the entire United Nations is very deeply involved. Political repercussions of failure of such a program, the most ambitious and costly public health campaign ever attempted, are self-evident. Nonetheless, reappraisal and reorientation toward malaria control rather than eradication is under way. The philosophic and practical differences between these two approaches are basic ones and must be fully appreciated for both their economic and epidemiological significance.

Epidemiology and Host Response

In our own smaller sphere, we have to advise and protect thousands of American tourists who in increasing numbers are going to Africa to visit game parks and who for the most part receive from their travel agencies no information on malaria prevention. Cases that appear among these highly vulnerable, nonimmune persons tend to be very severe, with a fatality rate of 10 percent among the patients with Plasmodium falciparum (malignant tertian) malaria.[2] Occasionally, we read of a returning veteran who suffers a suddenly fatal cerebral involvement from undiscovered (or "cured") falciparum malaria—a disease of the utmost danger (50 percent fatality rate), which demands instant life-saving therapy. We read, too, of new dangers to whole blood recipients[3] and of malaria transmission from shared narcotic addicts' needles.[4] Cases of imported malaria in the United States are summarized in a recent Center for Disease Control (CDC) surveillance report;[5] more general aspects of the problem have also recently been reviewed.[6]

In order to evaluate these problems and help you to assume your clinical responsibilities, I would like first to separate in your minds two distinctive patterns of host response to the same infectious agents. The first of these leads to endemic (or stable) malaria. This condition exists in an indigenous population that is repeatedly exposed to malaria from birth, with continuous high level of infection, but low manifest illness in the adult population. Those children who are exposed to malaria infection through infancy (and are among the survivors), are by the age of five years essentially immune to that strain of Plasmodium. Some investigators believe this degree of immunity is not possible among persons first exposed after the age of five years (which may include the patient presented here).[7] The suppressed manifestation of malaria among these "immune" persons may actually be passively acquired protection from mother's milk, followed by a resistance induced by a low-level prevailing infection ("premunition"). To treat such persons who are not severely ill could cost them their acquired protection. They then must return to their malarious homeland at considerable peril. Various degrees of endemic malaria have been described, based on the percentage of two- to nine-year-olds showing splenomegaly: Holoendemic (+75 percent), hyperendemic (50 to 75 percent), mesoendemic (11 to 50 percent) and hypoendemic (less than 11 percent).

Hypoendemic malaria is a characteristic of the second epidemiological pattern or host response to which I referred. It is typified by severe outbreaks, hence is called unstable, periodic, or epidemic malaria, and occurs in regions sporadically or periodically exposed, chiefly striking large numbers of nonimmune children. Occasionally, environmental or epidemiological conditions permit malaria to sweep over a region that generally has a very low level of infection, often with extreme virulence and, in the case of falciparum malaria, a very high death rate. This may be due to an unexpected increase in the population of the vec-

tor mosquito resulting from favorable breeding conditions, the sudden introduction of a better vector, human migrants carrying a different strain, or perhaps the mutation of the local strain to a more virulent disease agent. It also occurs when malaria is accidentally reintroduced in a region from which the disease had been eradicated, since eradication campaigns are designed only to interrupt transmission by infected mosquitoes and not to destroy the entire Anopheles population.

Whether a local upsurge of cases results from altered epidemiological conditions or from imported malaria, a highly vulnerable nonimmune host population will be affected, and this population consists mainly of the children born after the last epidemic or since local cessation of transmission. The resulting disease is what we call typical malaria. It is the only form most American clinicians see, though in fact it represents only a fraction of the existing cases. It is what we treat in an American soldier from Southeast Asia, a Peace Corps volunteer from South America, or a tourist returning from Africa. All display the host reactions of a nonimmune person—the classic or textbook syndrome of 48- or 72-hour fever and chills. The far more common suppressed infection (as opposed to disease) is seen in this country only in an occasional visitor or student from Africa. A comparable condition may be seen in a patient partially protected by chemosuppressant drugs. It also may be identified from tracing the sudden death from malaria of a blood transfusion patient to a "cured" or nonsuspected donor, one who subsequently (and often with difficulty) is proved to be infected.

Proper handling of a malaria patient, therefore, rests on careful determination of his history as well as precise identification of the disease agent. You must obtain and evaluate a thorough history of your patient's way of life—his place of origin and subsequent travels, the frequency and duration of his past exposures, and the probability of his returning to the same area. To this must be added genetic characteristics of your patient, as Blacks tend to be more malaria resistant than are Whites, and African Blacks are more so than American Blacks. The sickle cell trait and other hemoglobinopathies and glucose-6-phosphate dehydrogenase (G6PD) deficiency appear to be important factors in the pattern of natural selection for malaria resistance that continually occurs in highly endemic areas.

In holoendemic or hyperendemic regions—most of tropical Africa, Central America and tropical South America (except Venezuela), parts of Southeast Asia and Polynesia, much of southern India—malaria is one of the basic conditions that is part of and helps determine the way of life of the people. After childhood, the residents rarely suffer typical cyclic malarial fevers. Yet most of these populations are chronically infected, with plasmodia in the liver and only for brief periods in the bloodstream (presumably the bloodstream forms are cleared by antibody action and activated phagocytes).

It is not possible to tell whether this is a true immune response, an infection-immunity or premunition resulting in a chronic suppressed infection, or a condition induced by repeated reinfection. It does appear to represent a host-parasite balance marked by high gammaglobulinemia and splenomegaly in the human, and a low-level but viable infection capable of being transmitted to other biting anopheline vectors. Nonetheless, it is costly. The infected child, especially, is victimized. He suffers repeated energy-sapping bouts of fever and chronic anemia with a need for food energy to replace loss from fevers and for continual iron and protein replacement, occurring usually during the most critical first three years of life. This is particularly true if the maternal milk-protection is not sufficient, as is usually the case in malnourished populations. Frequently these losses are compounded by bloodsucking hookworms and other energy-demanding parasites. When malnourished infants suffer attacks of falciparum malaria, the eventual effect is a serious inroad on growth and mental development, with diffuse hepatic fibrosis and hepatomegaly.[8]

This is a yoke of quiet suffering seen throughout the tropics and subtropics. Evidence of illness is greatly reduced among adolescents, though healthy-looking children with falciparum malaria frequently have a heavy load of parasites in their blood. Adults in these highly infected regions, whether immune to or tolerant of their constant plasmodial guests, arc not measurably ill, though some may have a greatly enlarged spleen and possibly hepatomegaly as well. On the other hand, should they move into a different falciparum malaria region, they may contract a quite heavy new infection, though this appears not to be the case with the other species of Plasmodium.[8]

In hyperendemic falciparum areas we appear

to be dealing with human hosts who have built up resistance against a specific strain of this species and are protected by genetic factors, by some degree of acquired residual immunity to the local falciparum strain, and by a further degree of protection induced by premunition. Resistance against the other forms of malaria (vivax, malariae, ovale) is comparable, but these species of Plasmodium show less tendency to form a number of immunologically distinct local strains, so resistance is less geographically restricted.[8]

Despite the high degree of human adaptation to malaria, disease reactivation may be induced by stress, protein deficiency, age, concurrent infection, or a change of residence location (the latter in the case of falciparum malaria). Nonetheless, the pattern of tolerance that has evolved has enabled millions of persons to survive repeated infection with malaria (and a variety of other parasites), all competing for inadequate protein and food energy reserves. The so-called laziness of tropical living is more often than not this restriction of energy reserves, part of the adaptation to malaria. Despite vast expenditures and an unparalleled international effort, malaria remains the number one disease of mankind.

Control vs. Eradication

Retreat from the unduly optimistic WHO vision of world malaria eradication means that we now must face the prospect of developing a permanent (hence ultimately more costly) control program. This depends upon the reduction of malaria transmission to a tolerable level as a permanent obligation, one that does not involve the huge and often fruitless labor of removing the last vestige of infection within a prescribed period, usually seven to ten years. Many factors have combined to make that last 10 percent harder to achieve (and maintain) than the first 90 percent of malaria reduction. The problem is not caused simply by the rapidly growing populations of insecticide-resistant mosquitoes, by chloroquine-resistant Plasmodium falciparum, by movements of nonimmune or infected human populations from and into cleared areas, or by the difficulty in organizing, training, and supporting the mosquito spray teams in remote undeveloped tropical regions. Fundamentally, our failure to achieve eradication is a reflection of our failure to appreciate the range and diversity of ecological interactions in the epidemiological complex involved in malaria transmission.

The greatly increased selection pressure favoring drug-resistant strains of Plasmodium and DDT-resistant strains of Anopheles are expressions of the genetic flexibility of these organisms, just as is the human genetic response that has favored selection of malaria resistance or tolerance through selection of heterozygotes for sicklemia,, HbC, HbE, thalassemia, or of G6PD deficiency. But to this genetic adaptability of parasite, vector, and human host, we must add the enormous range of habits and species of Anopheles mosquito vectors involved—some 30 species in Malaya alone, perhaps 100 or so worldwide. Each vector species (or strain in many cases) has its own highly characteristic biting habits and food preferences, its own breeding locations and its own population dynamics with competing species, predators, and parasites. Often we spray for one mosquito only to find that another soon replaces it, perhaps with habits protecting it from DDT. An example is the replacement of an easily killed vector with a species or strain that does not land on household walls where spraying is concentrated. Just as we are discovering many unexpected repercussions of wide-scale application of DDT in agriculture, we are beginning to appreciate the variety of ways in which the epidemiological pattern of malaria transmission is expressed in different geographic areas and eco-systems. Therefore, a single pattern of control, based on a familiar transmission cycle, simply cannot be applied worldwide and expected to succeed.

Yet the feasibility of worldwide malaria eradication is based on the premise that a universal epidemiology, with only minor variations, is the general one: Infected (or susceptible) mosquitoes fly into a house, feed, rest on a wall or on furnishings and then fly off to rest, refeed at intervals (which permits development of the ingested sexual stages to infective sporozoites and their transmission), and finally lay eggs to complete their life cycle. So, one need only spray the house, inside and out, and the mosquito will land on it (before or after feeding), and then fly off to die. This method controls precisely those mosquitoes in the act of becoming infected or transmitting the agent. Maintain the residual insecticide, treat *all* infected humans, and local active transmission will be blocked, resulting in a dramatic drop-off of new cases. Continue this for several years, actively search for and treat all cases, and within five to seven years, all transmission will have been stopped and the Plasmodium (not the mosquito) will have been locally eradicated. Do this on a well-coordinated and

properly-funded national and international scale, and malaria will become a thing of the past.

In many areas this scheme has worked remarkably well. Malaria is essentially eradicated from the Mediterranean basin, its classic nidus. But in Malaya, for example, replacement vectors bite man outside of his home from inaccessible forest breeding sites. Elsewhere, mosquitoes bite inside houses but without lighting on the wall before or after feeding. Or they may bite only in forest sites. By a change of habits or replacement by other vectors or by other means, the vectors may circumvent our notion of where and how every self-respecting, proper Anopheles female *ought* to inoculate its human host with plasmodial sporozoites. We find that not only has resistance to DDT (and to nearly every other insecticide as well) been favored by natural selection in continuously sprayed areas, but also inherited behavioral patterns have been subject to natural selection, permitting survival of mutant forms or of different species possessing the favored traits.

The view that nature abhors a vacuum is correct. Eradicate one species, another will promptly replace it—and we seldom can predict which one. Nature is not only incredibly rich and varied, but enormously variable and adaptable as well. The small proportion of mosquitoes that escape the DDT assault can and, at a rapidly accelerating rate, will replace those that were eliminated. Complexity and adaptability is the "normal" pattern in nature, whereas our view is necessarily narrowed to specific human objectives reached by carefully prescribed methods along clearly marked and economically supportable pathways.

The assumption that what works some of the time must therefore work all the time against malaria has proved to be a catastrophic error in judgment, one that has involved vast effort and expenditure, and is now reaping increased disappointment and disillusionment. Hence the new efforts by WHO malariologists and others to make their attacks as adaptable as is their target. Control of malaria, as opposed to eradication, suggests survival within a balance, working within the system rather than attempting to destroy it Don Quixote-style in order to substitute our own system. We may yet discover that the same principle of parasite suppression rather than elimination applies to many other (but obviously not all) human infections as well. Controlled, low-level infections that permit development of tolerance, adaptability, premunition, or immunity may be preferable to total removal of every last infective agent. Our highly sanitized society with its hypersensitivity to any agent found dwelling within us is a reflection of the hothouse culture in which we live. We are obsessed with the need to obliterate any semblance of dirt, germs, microbes, worms, or vermin—terms that suggest roles we have defined for them and allocated as being in accord with *our* conception of life rather than theirs.

Lest this lead too far afield, I should like to return briefly to malaria and its presence, not in populations, but in *people*—your individual patients. If you were to treat an infected African who was living here for a short period, you should approach his case differently than you would that of an African who is here to stay. An American returning from Africa with falciparum malaria requires alert treatment oriented to the dangers that he faces in his nonimmune state. Not only does your patient require your keen attention—so does the health of others affected by him. In 1953, a Marine returnee from Korea spent a few nights camping ten miles from a Camp Fire Girls' outing. That night he was heavily bitten by locally abundant mosquitoes. It happened that these were Anopheles freeborni, a splendid malaria vector. (In 1833, this species was responsible for a wild epidemic that wiped out most of the Indians in the Central Valley of California; later, malaria was a scourge of the gold mining camps; about the turn of the century it was associated with irrigation in the Central Valley and made California the "most malarious state in the Union" with over 5,000 cases annually).[9] The slumbering Marine packed up the next day and went home; but before the summer was out, 35 girls from the nearby camp came down with vivax malaria, which fortunately did not remain as a viable focus of infection in the area.

Epidemiological insight with recognition of your patients' special requirements are part of the message imparted with the case of the patient presented here today. But this insight can only follow from your recognition that the problem exists or that it could exist in your practice. Without this mental preparation and anticipation, malaria will pass you by as it has nearly every physician who has initially treated with penicillin (for "flu") the malaria patients subsequently sent to CDC or to

major medical centers. The patient whose case was presented here is, unfortunately, a typical example. In an Army hospital, such misdiagnosis is rare, due to the physicians' expectations. Any patient seen by you who has been to an endemic malarious area within the previous five years (sometimes longer) should cause you to see over his head a red-flashing warning light blinking out the message: *malaria*. Recrudescent cases may develop two or more years after a Vietnam veteran's return, especially with vivax (benign tertian) or malariae (quartan) malaria. Even falciparum (malignant tertian) malaria, which is unique in that it does not continue to reproduce in the liver and thereby "reseed" periodic blood relapses, still may survive in infected liver parenchymal cells in an apparently suppressed state for 18 months (or longer in a few cases) before it breaks out into the bloodstream. It may, after such a delay, also appear in its pernicious and rapidly fatal form in the capillaries of brain, kidney, lungs, or intestine.

Pathology

Although all forms of malaria are uncomfortable and often temporarily disabling when a paroxysm strikes a nonimmune person, only Plasmodium falciparum, the agent of malignant tertian malaria, is life-threatening. Rarely, very young, severely malnourished children infected with P. vivax, P. malaria, or P. ovale may die of the malarial infection (or a combination of insults) or have severe anemia. More typical in these children is an insidious course of continuing relapse and reinfection with splenomegaly and chronic ill health. Among well nourished persons the sequence of relapses or reinfections is generally followed after about six months by an acquired immunity, or a state of premunition from successive exposures, or a combination of these. Despite much study of the subject, we can only say that resistance does develop, but the precise cause is still disputed.

Immunity is only effective against the blood forms, the merozoites released in cyclic waves that induce the 48-hour (tertian) or 72-hour (quartan) fevers. However, the liver stages (exoerythrocytic phase) are safe from the host's immune response. Hence, relapse originating from the liver hideout may occur over a prolonged period provided that the blood-based immune response has waned enough to allow a recrudescence of the erythrocytic schizogony. In cases of P. malariae the infection is particularly long-lived. The patient may show no sign of malaria for 25 years or more and then have a relapse, presumably from a reduction in the blood-based immunity. P. vivax relapse can occur seven years after the last exposure, somewhat less for P. ovale. These three species, the less pathogenic ones, can sustain the infection because of continuous merozoite multiplication in the liver, a secondary tissue schizogony that follows the initial growth of the parasite from sporozoites inoculated by an infected mosquito.

However, P. falciparum can undergo only a primary tissue schizogony. Sporozoites inoculated by the mosquito enter the liver parenchyma cells within an hour or two and undergo just two cycles of schizogony, rather than a continuous secondary series. Hence, it can be called the kill-or-cure malaria: once the illness is passed—and cured—it won't recur. However, a repressed infection from partially successful drug therapy or partial resistance to chemo-suppression may erupt a year or more afterwards. These are the "recrudescent" falciparum cases found among supposedly healthy or cured Vietnam veterans.

It is well that no true secondary liver schizogony occurs in falciparum malaria. The primary one is bad enough and is responsible for nearly all of the deaths and most of the severe sequelae—the "pernicious" form. This effect is caused by a peculiarity of the growing parasite within the red cell. The trophozoite's development modifies the nature of the host red cell wall, causing the infected cells to become sticky. The sticky cells tend to clump in capillary beds of internal organs (hence these stages are rarely seen in peripheral blood). Circulatory restriction, stasis or hemorrhage and necrosis of the affected area follow and produce a pernicious anemia. The clumped red cells tend to adhere to the endothelium of small capillaries, particularly where the capillaries suddenly narrow, as in the intestinal villi, kidney glomeruli, lung alveolar walls, and, of greatest threat, in the cerebral capillaries. The thrombosis is followed by leakage, local anoxia and necrosis causing nearly all of the characteristics of the malignant anemia including intestinal hemorrhage and mucosal sloughing, cardiac infarcts, kidney malfunction, jaundice and algid or other forms of cerebral malaria.

One additional form of falciparum malaria rarely encountered today, blackwater fever, is less well understood. It is a rapidly fatal hemolysis related to inadequate quinine treatment of falciparum malaria. Administering the drug to sensitized

persons may precipitate an often-fatal hemoglobinuria. Apparently the parasitized-quininized red cell acts as an antigen against which hemolysins form. Then a new attack of malaria, treated with quinine, provokes a crisis, causing intravascular hemolysis, renal tubular damage, renal cortical ischaemia, renal failure, profound anemia, and jaundice.[8] But since malaria therapy with quinine is rarely attempted, (see below) this man-made disease is largely historical.

Another malaria antigen-antibody complex associated with nephropathy does occur, however. This is the nephrotic syndrome or "quartan nephrosis" associated with cases of P. malariae in children and characterized by generalized edema and albuminuria at the early stages. It has been suggested that the parasite sensitizes the kidney and an auto-antigen is produced, with the antigen-antibody complex showing an affinity for the g'omerular basement membrane. Other observers have concluded that the tubular damage is degenerative and not inflammatory, causing nephrosis instead of a nephritis.[8] Early treatment will prevent the later irreversible changes and bring about a prompt cure.

Blood destruction leading to anemia is also far more severe with falciparum than with the other malarias. This is related to the type and number of red blood cells invaded during the erythrocytic stage. In falciparum malaria, 200,000 or more cells per cubic millimeter of blood may be destroyed. All ages and types of red cells are invaded. Overwhelming infections of 50 percent of the red cells may occur—though infections at half that level are usually fatal.[10] Vivax malaria tends to focus on younger red cells and seldom exceeds 35,000 cells per cu mm; malariae, the least destructive (except for the nephrotic syndrome), usually affects older erythrocytes, 5,000 to 15,000 per cu mm.

Treatment

Most cases of uncomplicated malaria will respond readily to 4-aminoquinoline therapy—chloroquine phosphate, 2.5 grams (1.5 gram base) over three days; and recurrence of vivax, malariae, or ovale malaria generally can be prevented by using the tissue-active drug primaquine phosphate (26.3 mg, 15 mg base) daily for two to four weeks. This is a secondary tissue schizonticide, the only one that can produce a "radical cure" for the recurrent forms. The latter drug should not be used in G6PD deficient persons (a trait more commonly found in Blacks than Whites in the United States) as it may induce severe, though temporary, hemolytic anemia.

If your patient is to spend a limited time in an endemic area where resistant falciparum is not a problem, chemo-suppression with chloroquine (500 mg once weekly) is essential, starting two weeks before and continuing *eight weeks after* leaving the endemic area. The Army weekly chemophrophylactic pill (chloroquine, 0.3 gram base, plus primaquine, 0.045 gram base) may be taken if the patient is not G6PD deficient. However, preventive therapy with primaquine can just as well be prescribed after his return (15 mg base daily for two weeks or for four weeks if the area is a focus of resistant malaria).

If your patient is heading for parts of South America or Southeast Asia where chloroquine-resistant falciparum strains are well established, "only the sulfones and sulfonamides are available to us at the present time as reasonably assured suppressives of multi-drug-resistant-P. falciparum," (reference 11, pp 739-40; *cf* also 12 for a broader review of resistance). The most widely used oral sulfone is dapsone (DDS). Another, diacetyl-DDS (DADDS), is given intramuscularly at intervals of several months. Chemo-suppression with DDS (25 mg) has been used either daily with chloroguanide or at weekly intervals with pyrimethamine or chloroquine plus primaquine.[7] Another oral combination, sulfadoxine (sulfomethoxine) 500 mg, with pyrimethamine 25 mg (adult dose), given at weekly intervals, has protected nonimmune persons in a highly drug-resistant area of Laos.[11] Fear over development of resistance among pathogenic bacteria caused by extensive use of sulfonamides for malaria prophylaxis has been a deterrent to wide-scale field testing of these drugs.

Curative treatment of chloroquine-resistant falciparum malaria among nonimmune persons who have access to supervised treatment requires a 14-day quinine regimen. Three treatment schedules have recently been described (reference 11, p 741) using quinine sulfate, 2 grams daily for 14 days, alone or with pyrimethamine and/or various sulfa or sulphone compounds. Most critical is the immediate life-saving treatment of pernicious malaria with cerebral involvement. Cerebral involvement is indicated by falciparum infection with various central nervous system manifestations: Deepening coma (if entire cortex is involved); hemiplegia or Jacksonian epilepsy (motor area);

algid malaria (pituitary and adrenal involvement); hyperpyrexia (to 42°C)—involving thermo-regulatory centers in the pons; bulbar paralysis (hind brain); tremors (basal ganglia), etc.—depending upon the region of the brain affected.[8] Treatment for this and other forms of pernicious malaria (responsible for capillary thrombi or stasis, leading to hemorrhage from leaking vessels, tissue anoxia and necrosis) should be intravenous quinine dihydrochloride (0.6 gram in 300 ml saline solution over at least 30 minutes every eight hours for a maximum of three doses). Catchpool[7] suggests preceding the intravenous quinine with a glucocorticosteroid (dexamethasone, 4 to 6 mg every four to six hours). Similar emergency measures are required for pernicious malaria of the intestinal tract, leading to hemorrhage into the lumen, mucosal sloughing, and rapidly fatal dysentery. Endothelial involvement of cardiac tissue and renal glomerulonephritis are other forms of rapidly fatal pernicious falciparum malaria.

Prevention and treatment of drug-resistant malaria are limited and imperfect; and they are under intensive and often frustrating research, involving a number of drugs in a variety of combinations. New procedures are developed and tested, only to be compromised or blocked by new forms of resistance or untoward drug reactions. Clearly we need new and more effective antimalarials—a very different view from those blissful ones held ten years ago. Malaria specialists in those days were apt to complain that we would be hard-pressed to find good examples of malaria for study and that we would never again be able to wrestle with the fascinating problems associated with intracellular malaria parasites. It reminds one of the early stages of the DDT-honeymoon, when houseflies, it was thought, soon would be relegated to pins in museum trays. That was in the days before the advent of the 1973-model Superfly. Present-day mosquitos suggest a similar future, as do the strains of Plasmodium they transmit. These evolutionary changes in our own lifetimes reemphasize a lesson we seem destined to re-learn continually: Living things do not serve man alone, nor do they follow the laws or read the textbooks we write about them. Instead, they form continuously changing, adapting, interacting, and interdependent communities that are oblivious to our special needs or wishes.

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Important Advances in Clinical Medicine

Epitomes of Progress—Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

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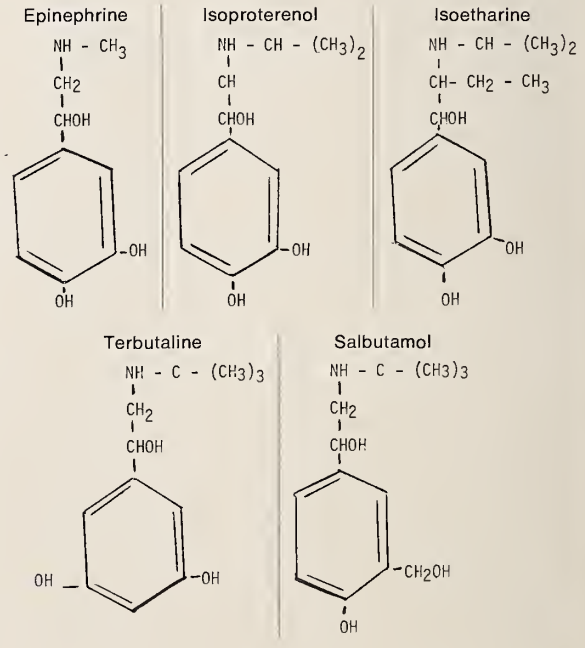
The New Beta Stimulators

—Better as Well as Newer?

THE CONCEPT OF SEPARATE β_1 (for cardiac stimulation and certain metabolic effects) and β_2 (for vascular and bronchial smooth muscle relaxation) adrenergic receptors has led to the search for selective beta receptor stimulating agents. Although epinephrine and isoproterenol are excellent bronchodilators, their β_1 stimulator properties produce the undesired effects of tachycardia, palpitations and arrhythmias.

At least two new compounds, salbutamol and terbutaline, designed to be more effective β_2 stimulators, have been undergoing extensive clinical trials. A comparison of their chemical structures with those of the more familiar drugs is shown in the accompanying chart.

Note the tertiary butyl group on the nitrogen which apparently prevents the activation of mono-



mine oxidase that occurs with the other three. This substitution allows for longer action, gives greater bronchial than cardiac effect, and permits oral administration. Additionally, alterations of the catechol structure restrict the action of another enzyme, catechol-o-methyl transferase, and thus adds to the prolonged activity of these new compounds *in vivo*.

Salbutamol and terbutaline have been demonstrated to be potent bronchodilators by any of the five routes of administration—by vein, subcutaneously, sublingually, by aerosol, or orally. They have somewhat decreased effects on heart rate and systolic pressure when compared with comparable doses of isoproterenol. They have prolonged action up to five hours. In a double-blind study which compared both drugs orally with a placebo in 12 patients with asthma, they were equally effective in lowering the forced expiratory volume and did not adversely affect arterial gas tensions. Fine tremors have been the most frequently reported side effect (in up to 30 percent in one study) while palpitations were noted in some 14 percent of persons.

Interestingly, no central nervous system effects were found in animal studies or reported in the clinical trials.

If these new drugs are to represent significant advances in the symptomatic relief of asthma, they must prove to offer more than epinephrine by parenteral route, isoproterenol by inhalation or ephedrine orally. To do this they should at least demonstrate (1) equivalent bronchodilation over a longer period and with less side effect and (2) less tachyphylaxis or refractoriness after repeated use.

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Clinical Uses of Transfer Factor

TRANSFER FACTOR is a dialysable extract of sensitized lymphocytes which transfers delayed sensitivity from a skin test positive donor to a skin test negative recipient. It is exceedingly potent: the extract derived from 0.1 ml of packed leukocytes from a sensitive donor is sufficient to transfer reactivity. The dose used for therapeutic purposes is far in excess of that necessary to simply transfer skin reactivity. It is only cellular immunity, not antibody formation which is transferred by this means.

Transfer factor therapy has been used in over 30 patients with the Wiskott-Aldrich syndrome, and about half of them show clinical benefits as evidenced by reduced frequency and severity of infections, reduction of splenomegaly, and by the production of migration inhibitory factor (MIF) to specific antigens, but no increase in lymphocyte DNA synthesis in response to the same antigens. Unexpectedly, three patients showed improvement in bleeding without significant changes in the platelet count following transfer factor therapy. A defect in the monocyte IgG receptor has been identified in some patients, and it is in these patients that a favorable response to transfer factor has been noted, suggesting that there may be two distinct forms of the disease.

Two out of three patients with Swiss-type agammaglobulinemia showed conversion of skin reactivity following transfer factor therapy and in one of these patients in whom it could be measured there was also MIF production. Thus it is possible for transfer factor to act even in the absence of mature T cells.

Results in the therapy of mucocutaneous candidiasis are variable. Some dramatic effects have been reported, but some patients seem not to be benefited, even by repeated large doses of transfer factor from candida-immune donors.

Current investigation involves the use of transfer factor in patients with disseminated infections such as coccidioidomycosis and generalized vaccinia, in patients with immune deficiency diseases and absent delayed sensitivity, and in patients with metastatic malignancy, especially those with malignant melanoma.

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Newer Mediators in Allergic Diseases

WHILE HISTAMINE has long been established as an important mediator in human immediate hypersensitivity, the role of other pharmacological mediators has only recently emerged from experimental studies using human tissues, sera or secretions. Thus in addition to histamine, slow reactive substance of anaphylaxis (SRS-A) has been found to be released when chopped human lung tissue was passively sensitized with human reaginic serum (IgE) and challenged with ragweed antigen *in vitro*. SRS-A is probably a significant mediator in human asthma. This may explain why antihistamines alone play little, if any, role in the prevention or therapy of bronchial asthma. Using the same *in vitro* system, it was found by Kay and Austen that another mediator, ECF-A (eosinophilotatic factor of anaphylaxis) is also released which attracts eosinophiles to the site of the reaction. The actual role of ECF-A in human disease is still uncertain. When basophil leukocytes from allergic patients are reacted with antigen or anti-IgE, a factor is released which aggregates rabbit platelets causing them to release their histamine. This factor, called platelet activating factor (PAF), is obtained by breakage or autolysis of human and rabbit leukocytes and may be instrumental in the deposition of circulating complexes in Type III immune complex human disease.

Bradykinin was also recently demonstrated in the edema fluid of the characteristic wheal and flare skin test lesion mediated by reagin or IgE and in the nasal secretions of patients with ragweed hay fever. This suggests a possible role of bradykinin in Type I immediate hypersensitivity in man.

Finally, a member of the prostaglandin (PG) family, $PGF_2\alpha$, was demonstrated to exert constriction on human isolated bronchial muscle. As $PGF_2\alpha$ occurs in human lung, it may play a role in bronchial asthma.

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Benveniste J, Papoiah R: Platelet activating factor: Its release from human and rabbit leukocytes by a reaginic hypersensitivity mechanism. Fed Proc abst 3001, 1972, p 748

Modifications of Antigens Used in Immunotherapy

IMMUNOTHERAPY ("allergy injections," desensitization) has been for years an accepted method of treating inhalant allergy. The usual aqueous allergen extracts, while effective if used appropriately, have at least two drawbacks. First, benefit is directly dose-related, yet attempts to give the patient large amounts of rapidly absorbed allergen may produce severe reactions, and, second, injections need to be given at intervals of days to weeks for long periods.

Efforts to overcome these undesirable features have been in the direction of altering the allergen so that the patient can tolerate more, and of decreasing the rate of absorption and prolonging the effect of allergens after injection.

Aqueous extracts emulsified with mineral oil are absorbed slowly, and should theoretically allow both higher doses and longer intervals between injections. Although in use for ten years, the method is still under study because of problems encountered with the oil, which tends to act as a foreign body in certain patients and has oncogenic properties in animals. Alum-precipitated pyridine extracts, in current use, are absorbed slowly and require fewer injections. Their effectiveness appears to vary with the allergen, and careful evaluations of the effectiveness of all such antigens have not yet been performed. Recently a new kind of alum-precipitated ragweed extract has appeared, but this allergen is not clinically significant in California.

Prolonged incubation of grass pollen extract with formalin and other substances has been performed in an attempt to reduce the allergic potential of the antigen while leaving unimpaired its capacity for producing protective antibodies. This "allergoid" material has been tested so far only on animals and non-allergic human beings, but it represents another promising approach to the problem of giving the patient larger amounts of active allergen with less risk of provoking severe symptoms.

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Current Status of Provocative Food Testing

PROVOCATIVE FOOD TESTING was revived and popularized by Rinkel and Lee in 1960, and the technique has had numerous proponents since that time. The method, however, remains controversial and is not generally used in the diagnosis of food (or other) allergy by most allergists. The testing procedure consists of the intradermal injection of a food extract of potency and volume sufficient to induce systemic symptoms, followed by the immediate injection of a small amount of the same food extract to neutralize the symptoms. Duke, in 1921, described a similar procedure in which food extracts were used to produce symptoms in patients with gastrointestinal and genitourinary complaints followed by neutralization of the symptoms with epinephrine. A recent modification of this procedure utilizes sublingual administration of food extracts or other materials. Advocates of these methods claim an accuracy of up to 85 percent in identifying specific food sensitivity. Such advocates also state it is imperative that the patient have complete evaluation of inhalant allergy to pollens, dust, molds, and epidermals, and that environmental allergen control is essential before food testing.

Long overdue objective scientific evaluation of these provocative-neutralizing techniques is now being performed. The validity of the technique was not established in one recent study of 20 patients with food allergy.

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Inhibition of Histamine Release by Cyclic 3′, 5′-Adenosine Monophosphate (CAMP)

THERE IS MUCH REASON to believe that exposure to antigen produces allergic symptoms, such as asthma and allergic rhinitis, by stimulating the release of histamine and slow reacting substance of anaphylaxis (SRS-A) from IgE-sensitized blood basophiles or tissue mast cells at the target or shock organ sites.

In examining the mechanism involved in the antigenic release of histamine and SRS-A, it has been learned that materials such as isoproterenol, theophylline, dibutyryl CAMP, and prostaglandins E_1 and E_2 which mimic or increase the cellular content of CAMP also inhibit the release of histamine and SRS-A from human lung tissue or leukocytes. Other leukocytic functions, such as the killing of target cells by lymphocytes and lymphocytic transformation, are also inhibited by these materials.

In the many cellular systems in which CAMP has been studied, it usually functions as a "second messenger" to promote a hormone-induced *stimulating* action. The *inhibition* of allergic histamine release by CAMP stands as an interesting contrast.

Further studies of the histamine release mechanism, however, are clearly needed since other materials such as cholinergic agents disodium cromoglycate and diethylcarbamazine, which also inhibit allergic histamine release, apparently have no influence on cellular CAMP levels.

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Status of Testing for Penicillin Allergy

ANAPHYLAXIS and other allergic reactions continue to be a major concern to all those administering and receiving penicillin therapy. Skin tests with penicillin G and several of its derivatives appear to be the simplest and most practical way to predict allergic reactions to penicillin. The major antigenic determinant derived from penicillin G is penicillenic acid which, through the penicilloyl (BPO) radical complexed to body protein, acts as a sensitizing antigen for the stimulation of antibody production. IgE anti-BPO antibodies are thought to be responsible for penicillin-induced urticaria and reactions of serum sickness type. Penicilloyl polylysine (BPO-PPL) skin tests detect these IgE antibodies, while BPO-PPL hemagglutination tests detect IgM and IgG antibodies. Minor antigenic determinants derived from penicillin G, including penicillenate, penamaldate, penicillamine and penicillin G itself can induce IgE antibodies important as causes of anaphylactic reactions. These IgE antibodies may be detected by skin tests with a minor determinant mixture (MDM). Clinical studies have demonstrated that

only 14 to 27 percent of patients with a history of penicillin allergy may actually have IgE antibodies. In patients with negative skin tests with both BPO-PPL and MDM, penicillin administration has not caused immediate or accelerated allergic reactions. Since neither MDM nor BPO-PPL are commercially available, routine skin testing is still not possible. Until these reagents become available, clinicians must rely on the patient's history despite its fallibility.

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Bronchiolitis—A Stage of Incipient Bronchial Asthma?

Bronchiolitis is an important cause of acute lower respiratory tract disease in infants. Hall marks of the disease include: (1) an acute onset of respiratory distress with sibilant rales and wheezes, (2) evidence of obstructive pulmonary hyperinflation clinically and by radiologic examination, (3) normal temperature or low-grade fever, (4) absence of past history of wheezing. A viral infection, particularly respiratory syncytial virus, is thought to be the most important cause. Differentiation from bronchial asthma is not easy, since bronchial smooth muscle responsiveness to bronchodilators is not good in this age group. Retrospective studies have suggested that in 30 to 50 percent of children with bronchiolitis, bronchial asthma develops later in childhood.

Two recent prospective studies revealed that 50 percent of these children, when followed five to eight years after the initial episode, had recurrent wheezing. Important prognostic indicators include: (1) positive family history of atopy, (2) other allergic manifestations (for example, hay fever, atopic dermatitis), (3) nasal eosinophilia, and (4) significantly positive reaction to skin tests with common inhalant allergens. It is postulated that patients with an atopic diathesis are more likely to have wheezing with a viral respiratory infection. However, further epidemiological work on the effects of respiratory viral infections on the non-atopic patients is needed to confirm this impression.

These studies strongly suggest that bronchiolitis is frequently followed by asthma, particularly in infants with other markers of the atopic state. Prophylactic measures aimed at lessening allergenic exposure at this critical period should be evaluated to determine whether the prognosis can be altered.

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Pitfalls in the Use of Skin Testing in Allergy

Two recent reports deal with some of the pitfalls in allergy skin testing. One of these reemphasizes what has been known for some time but is often lost sight of—that positive skin tests alone do not reflect active clinical allergy. Whitcomb tested 50 medical students, taken at random, for sensitivity to nine inhalants and eight food allergens. Almost two-thirds of them (32) had positive reactions (two plus or more). In all there were 100 such positive reactions, 84 to inhalants and 16 to foods. No one reacted to food tests alone. Only about half (17) of the 32 who had positive tests had experienced clinical symptoms in the preceding year. The discovery of positive reactions came as a surprise to the other half. It would seem that either their challenge with the antigens concerned was insufficient or some other factor in the allergic response was missing.

Allergists have differed in their opinion about the extent to which drugs used in treatment of allergic disease affect skin tests. The matter has recently been reinvestigated. Hydroxyzine, (Atarax®, Vistaril®), diphenhydramine (Benadryl®) and chlorpheniramine (Chlor-Trimeton®, Teldrin®) produced significant skin test inhibition. The effect of hydroxyzine was profound at one hour after drug administration and was still present at 24 hours. Ephedrine, aminophylline and prednisone had no effect on the skin tests. It is concluded that antihistamines and hydroxyzine should be discontinued for at least 24 hours before skin testing.

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A Critical Appraisal of Recent in vitro Diagnostic Tests for Allergy

SEVERAL *in vitro* TESTS based on the detection of IgE antibodies in allergic patients have been recently proposed. Histamine release from the patient's basophile leukocytes upon challenge with suspected allergens, while still a laborious research procedure, reflects both specific IgE content in the serum and the state of cellular sensitivity of the patient, and as such may correlate better with clinical sensitivity than tests based on detection of specific serum IgE alone such as the rat mast cell test and radioimmunoassays. The rat mast cell degranulation test is also still a research procedure. It is subject to several technical limitations and has not yet been subjected to critical statistical analysis using the results of tests on large numbers of actual patients with many antigens. Furthermore, this test is not significant unless it is performed with adequate controls and with several serial dilutions of the serum and the antigen. These factors appear to preclude its routine practical use because of time and expense. Assaying the histamine released from rat mast cells would make the test more quantitative; however, there does not seem to be a simple relationship between morphological criteria of mast cell degranulation and histamine release. All these factors seriously limit the clinical significance of the rat mast cell degranulation test at this time.

Sensitive radioimmunoassays capable of detecting minimal amounts of specific IgE seem to be more promising. However, they are still mainly elaborate research procedures which must also await results on large numbers of patients with more antigens.

Finally, any *in vitro* or *in vivo* test which demonstrates the presence of any antibody including IgE cannot be accepted by itself as evidence for an etiological role played by that antibody in clinical situations.

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EDITORIAL

Of Racial Minorities in Medical Education

THIS NATION was founded nearly two hundred years ago on the proposition that "all men are created equal." Unfortunately what was meant by "equal" is not defined in the Declaration of Independence, and the interpretations have varied from political equality at the ballot box, through equal opportunity for education and advancement, to equal participation in every aspect of American life including all the goods and services of the gross national product. Equal participation has lately been receiving particular emphasis in health care. This is clearly evident in the efforts of both the public and private sectors to overcome any and all barriers to access to medical care and to make high quality health care equally available to all. Along with this there is now a nationwide determination to make the racial balance of health manpower more nearly match the racial balance in the society to be served. In fact there seems to be some kind of national imperative to accomplish this goal.

America has always been a melting pot. The current thrust is simply adding more heat to the melting process. It is not so very long ago that the Irish, Italians, Poles, Chinese, Japanese and Jews were looked upon as minorities and all were victims of many social and racial injustices. Now the Blacks, Latinos, Chicanos and those called "Native Americans" for want of a better term occupy the limelight as disadvantaged minorities. It is very proper and long overdue that the injustices which many among these minorities have endured be corrected, but it is also true that the heat which is being applied to accelerate this process is itself producing many new problems and some new injustices as well.

The main issues may be examined around the question of who is to be admitted to medical school and eventually to become a physician serving society. Two imperatives appear now to exist. There is the traditional one that anyone who is graduated from medical school must meet high standards of professional competence, and now another that the racial balance among physicians should more nearly match the population to be served. Equal opportunity is the byword, but to what extent is equal opportunity or one's civil rights upheld or compromised, when a decision is made to give a place in medical school to someone from a racial minority with a "different" social and educational background and to reject for this place someone else who is admittedly well qualified by traditional standards? Is it individuals who should have equal opportunity, or is it something else deemed more in the national interest? Questions such as these are not yet answered. In fact there are laws on the books which prohibit any sort of racial discrimination in the educational system while at the same time the Federal Government is beginning to demand evidence of "affirmative action" to achieve not only racial but, more recently, sexual balance throughout the educational system, and is starting to make this a requirement if an institution is to receive federal funding.

It has been said that America has become the first large nation in history to make a really serious effort to try to eliminate racial inequality, and it now seems clearly willing at least temporarily to pay a price in reverse discrimination and reverse injustice to accomplish this. This is reflected in what is taking place in the medical schools of California and elsewhere. And it has the official support of organized medicine. More than two years ago the Council of the California Medical Association adopted a "Policy Statement on Admission of Minority Medical Students" which urged each medical school in California to have an active program to expand the minority student enrollment in each entering class. Elsewhere in this issue (page 80) is a progress report on what has been accomplished with respect to the identical criteria adopted at that time by the Councils of the CMA and the Golden State Medical Association. The achievement so far has been impressive.

But no one wants progress toward equal opportunity and racial equality in medical education to be accomplished at the sacrifice of excellence and

professional competence of all medical school graduates whatever their race or educational backgrounds. This is an even greater responsibility than "affirmative action" for medical educators, and for this medical schools will be held fully accountable. It is disturbing to sense that what is now occurring in medical schools may be fraught with some danger and raise some uncertainties about the assurance of excellence. The traditional methods of selecting candidates for admission to medical schools are obviously being modified to serve a broader social purpose while at the same time the traditional curriculum is undergoing what appears to be radical revision, as are the traditional methods of examining students to determine the extent of their understanding and competence. These innovations, occurring together as they are, at least suggest that excellence may be in some jeopardy.

Racial balance in medical schools is a goal to be achieved, and so is excellence. There is measurable progress toward the former with as yet to be measured effects upon the latter. The minority students who have recently been admitted with different or disadvantaged backgrounds have yet to graduate. When they do, there must be no question of their excellence or competence. It is imperative upon medical educators to accomplish this and upon the medical profession to be satisfied that they do. The public, of all minorities and all races, has the right to expect no less of its physicians. The CMA leadership and the medical school deans in California must see to this.

—MSMW

Housestaff Membership Merger for the Future

DURING THE PAST TWO YEARS, several reports and resolutions have appeared in the American Medical Association House of Delegates urging state associations to establish active voting membership for interns and residents. Quietly in California, the thoughtful evaluation of this housestaff membership had already begun. The California Medical Association had set the wheels in motion before the recent "bandwagon." The CMA Commission on Communications' Subcommittee on Interns and Residents with Dr. Ralph M. Milliken as chairman, had begun a studied evaluation and development of recommendations to bring housestaff into active membership. The recommendations that came from that work, as passed by the CMA Council on January 5, 1973, for transmittal to and consideration by the 1973 House of Delegates, are printed elsewhere in this issue of CALIFORNIA MEDICINE. The committee has based its recommendations on the objectives of the CMA and input from housestaff, from county society officers and executive directors, and from the Committee on Organizational Review and Planning.

These recommendations are a CMA investment in its future. There are about 5,000 housestaff in California and most will stay here to practice. Through forming ties early in training, young physicians should develop bonds that will last the full professional career and will help to maintain a large, strong state medical association.

The recommendations recognize that housestaff, as licensed physicians essentially engaged in primary care, have multiple educational and patient-care problems. Interns and residents need a professional association like the CMA as our advocate, although we are not often likely to acknowledge that need. More and more we recognize the limits of a single housestaff association to improve training and patient care. Since our concerns find parallels in the community, the CMA is a natural as our advocate. In addition, current national legislation, notably H.R. 1 (the PSRO bill) does not distinguish between medical school and community hospital. The law and its mechanisms apply to us both.

In return for advocacy, housestaff can contribute much, beyond simply the energy of youth, to the vitality of the CMA. The changes in medical education have developed a generation of physicians with extra-medical interests. The medical association may find housestaff bringing new expertise of various sorts to its committees. The effect can only further improve health care.

The recommendations passed by the Council focus on CMA membership for interns and residents, but they structure that membership to mesh with county society membership. The CMA membership would be active, voting, with the privilege to hold office. There would be proportional representation in the CMA House of Delegates. The

While a medical student at Stanford University School of Medicine, the author was a student member of the CMA Committee on the Role of Medicine in Society. He now is the Delegate of the AMA Interns and Residents Business Session to the House of Delegates of the AMA, June 1972 to November 1973. His initial contact with organized medicine was through the Santa Clara County Medical Society.

recommendations begin now but retain the flexibility of allowing natural development, especially of ties with the county medical societies. There are also points of reevaluation that may be seen as providing further flexibility.

The importance of these recommendations goes far beyond California. They will serve as a model in other parts of the country. The February 1973 AMA National Leadership Conference used the California recommendations as a basic model in its seminars on housestaff membership. Thus, the CMA becomes a pacesetter.

Through the recommendations, two large groups of physicians can be brought together under one roof. As the relationship grows, it can be expected that the two not-too-disparate groups will see how similar are many of our problems and goals. The result should be a strong, democratic and unified profession which can best meet future problems in health care.

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Illicit Intravenous Drug Use and Bacterial Endocarditis

INFECTIOUS DISEASES of many kinds are common among the consequences of illicit intravenous administration of drugs, especially narcotics. Infective endocarditis is clearly one of the most serious of such infectious complications. There is an added significance in that infective endocarditis has never been a common disease. Indeed, it might be expected to decline in frequency with time. As acute rheumatic fever becomes a rarity, the residuum of rheumatic heart disease should also diminish and the population of vulnerables should become smaller. Among remaining antecedents, however, it now appears that illicit intravenous drug use is of increasing importance.

The report of Rosenblatt and co-workers in this issue of CALIFORNIA MEDICINE supports reports by other observers in affirming there is a higher proportion of addicts among patients recently admitted to hospital with infective endocarditis. An additional ominous change is also documented, namely, an increased incidence of endocardial infection caused by enteric, Gram-negative bacilli. At least two aspects of this development merit additional comment.

First, there is the poor outcome with antimicrobial drug therapy. The use of standard drugs, new agents, and novel combinations of antimicrobics has resulted, at best, in suppression of the infection. Cures are rare. At present, surgical debridement under cover of suppressive antimicrobial therapy appears to be the most useful approach.

Second, there is the enigma of pathogenesis. Despite the common occurrence of enteric, Gram-negative bacilli as causes of bacteremias, endocardial localization is distinctly uncommon—quite unlike the situation with Gram-positive cocci. It has been suggested that differences in the humoral immune response are of importance.[1] The enteric, Gram-negative bacilli typically activate a complement-mediated, bacteriolytic system, whereas the Gram-positive cocci stimulate agglutinins/opsonins without the involvement of complement. However, in the case of Pseudomonas and Serratia, bacteriolysis does not appear to result with humoral immunity. Moreover, abnormally high concentrations of immunoglobulins and serologic reactivity with an array of antigens (apparently unrelated to the disease or immunization history of the patient) are characteristic of serums from narcotic addicts.[2] Possibly, these immunoglobulins serve to facilitate endocardial localization of enteric, Gram-negative bacilli that are injected intravenously along with illicit drugs. Valvular damage, as attested by earlier episodes of bacterial endocarditis, was certainly of pathogenetic significance in two of the three patients reported by Rosenblatt et al.

Although bacterial endocarditis, as contrasted with other kinds of infective endocarditis, is usually curable through the proper use of antimicrobics, the challenge of devising and applying effective therapy is multiplied in addicts. So also is understanding the possible pathogenetic significance of hyperimmunoglobulinemia.

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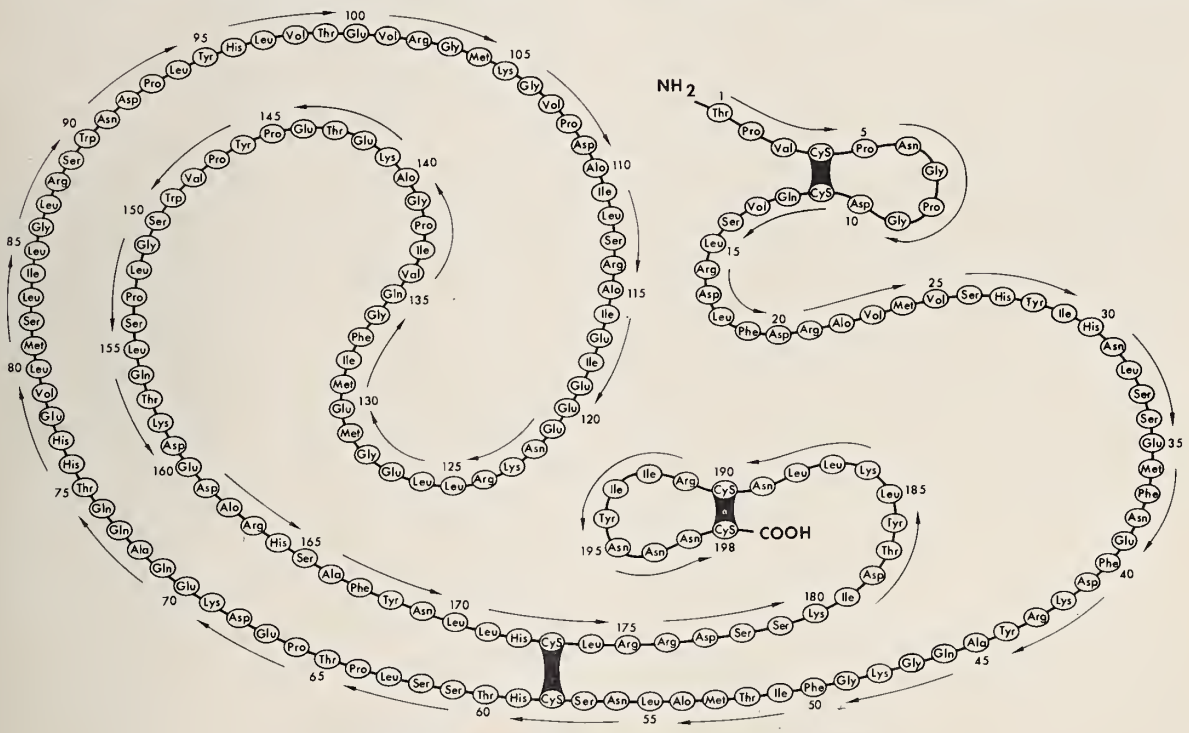
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Prolactin

THE FIRST INDICATION that a hormone of the anterior pituitary might effect lactation in mammals came from the experiments of P. Stricker and F. Grueter in 1928. Later, O. Riddle reported growth of the crop glands of pigeons after the injection of pituitary extracts. Subsequent work indicated that this effect in birds is due to the same hormone that induces lactation in rats and rabbits. Lactogenic activity has been reported to be present in the pituitary extracts of various species, including humans, sheep, cattle, pigs, horses, whales, rabbits, cats, rats, guinea pigs, mice, fish, amphibians, reptiles and birds. Highly purified prolactin preparations were obtained from cattle and sheep pituitary glands by a number of investigators during the period of 1937-1955. The sheep prolactin molecule is a protein consisting of 198 amino acids with a molecule weight of 23,000; the exact arrangement of these amino acids in definite sequence (see chart) was discovered in 1969 by scientists of the Hormone Research Laboratory on the San Francisco campus of the University of California.

Since the isolation of the growth hormone (HGH) from the human pituitary glands in 1956 and the demonstration of its intrinsic lactogenic activity in 1961, attempts to obtain from extracts of human pituitaries a distinct preparation which chemically differs from HGH and possesses only lactogenic activity have been unsuccessful. However, J. L. Pasteels, W. H. Daughaday, A. G. Frantz and others gave evidence for the existence of prolactin in the human gland from histological, clinical and biological studies. The final proof of its existence came from the isolation of human prolactin (HP) in highly purified form by U. J. Lewis, H. Friesin and their co-workers in 1971. HP and HGH exhibit overlapping biological activities: For each milligram, HP possesses 25 international units (IU) of lactogenic activity and 0.4 USP units of growth-promoting activity, whereas HGH has 2 IU of lactogenic activity and 2 USP U growth-promoting activity. They also have similar molecular weight. A single human pituitary gland contains approximately 0.02 mg HP and 10 mg HGH. In light of these data, it is not surprising there



Amino acid sequence of the ovine prolactin molecule

was delay in recognizing the definitive existence of the prolactin molecule in pituitary glands of humans.

Human prolactin has now been isolated and identified. It is important to elucidate its amino acid sequence. A previous comparison of the primary structures of HGH and sheep prolactin indicated a high degree of homology and suggested that these two molecules must have evolved from a common ancestor. It would be of great interest to compare the amino acid sequence of HP with that of HGH. This comparison may also provide an explanation of the intrinsic lactogenic activity in the HGH molecule.

Prolactin is remarkable in its broad spectrum of biological activities among the vertebrates. The role of prolactin in mammary-gland development and function has long been recognized. It acts as a synergist with steroid hormones in the sequential development of ductal and lobuloalveolar components of the mammary tree (mammogenic action). Secretory activity is also dependent upon the action of prolactin in synergism with adrenal hormones to initiate milk production (lactogenic action) and to maintain and augment it (galactopoietic action). In birds, two of the most striking actions of prolactin are stimulation of crop "milk" formation in pigeons and doves and induction of brood-patch developments in a variety of species. Prolactin caused increased body weight in tadpoles. For fresh-water fish, prolactin is essential for the survival of osmotic stress. In efts, prolactin induced the land-living stage of this species to return prematurely to water. The water-drive activity of prolactin is also seen in salamanders. Thus, the versatility of prolactin raises an important question: What are other functions of prolactin in human subjects besides its role in the mammary-gland development and function?

In experiments with animals, prolactin is found to be one of the factors involved in the growth of mammary carcinoma. Does HP play a role in the initiation and maintenance of breast cancer patients? There is evidence that prolactin induces the growth of prostate glands in some laboratory animals. Does HP play a role in the initiation and maintenance of normal and/or abnormal growth of prostate glands in man? Investigations on human prolactin in the next few years will undoubtedly provide us interesting and exciting data of its physiological functions in health and disease.

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CASE REPORTS

Refer to: Schwartz WL: Hypothyroidism and Addison's disease totally corrected by adrenal replacement therapy. Calif Med 118:57-60, Feb 1973

Hypothyroidism and Addison's Disease Totally Corrected by Adrenal Replacement Therapy

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THE COEXISTENCE of multiple endocrinopathic conditions has been increasingly studied over the past ten years. When Gastineau and Arnold[1] reviewed 538 patients with Addison's disease, about 2 percent (11 cases) were noted to have had thyroid failure also. Two of these patients with mild clinical myxedema became euthyroid after adrenal replacement alone. One similar case was reported by Borghi.[2]

The patient described here had myxedema and Addison's disease concurrently. Subsequent adrenal replacement therapy alone corrected the hypothyroidism as well as the Addison's disease.

Report of a Case

The patient, a 44-year-old Caucasian woman nurse, was admitted to the hospital 15 November 1969 with a history of weight loss and progressive weakness over the past year. She had been sleeping 12 hours a night and awakened feeling tired. Nausea and anorexia developed and she had lost 30 pounds in the year before admittance. She ate mostly soups but did not crave salt. Cold intolerance had become pronounced recently, although the patient had had it to some extent for several years. Her axillary hair had become scant and she no longer needed to shave under her arms as she had done regularly before. She had menstrual periods but light flow. Libido had declined during the latter months of illness. Constipation had been a longstanding problem. She had had vitiligo about the eyes and vulva area for at least ten years; and recently she noticed increasing generalized brown pigmentation of her skin, making the areas of vitiligo more prominent by contrast. It is interesting that diabetes requiring insulin had recently developed in the patient's daughter, aged 16, although there was no known history of diabetes on either side of her family.

On physical examination the patient appeared chronically ill. She had gray, rather fine hair, a decided tan over the entire body with numerous dark freckles and areas of depigmentation about the eyes and vulva. She moved slowly and although she answered questions well, her responses were considerably delayed. Blood pressure was 90/70 mm of mercury recumbent, and 65/50 erect (with a "light-headed feeling"). The pulse was 76 and regular. Visual fields were intact by confrontation. No abnormality of mucous membranes were noted and there was no thyroid enlargement or tenderness, no cervical or other lymphadenopathy. The abdomen was normal to palpation. A right lower quadrant surgical scar (appendectomy at age 19) revealed no pigmentation. Heart sounds were distant and quiet. Peripheral pulses were weak. Except for the previously mentioned vitiligo about the vulva, pelvic examination was unremarkable. Muscle tone in the extremities was poor and veins were notably flat with limbs dependent. Results of neurological examination were essentially negative except for delay in the relaxation phase of the deep tendon reflexes and the already noted slowed response.

Laboratory studies

The blood cell count was remarkable in that there was relative lymphocytosis with 6,500 leukocytes per cu mm and a differential of 37 percent polymorphonuclear cells, 1 percent eosinophils, 4 percent monocytes and 58 percent lymphocytes.

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Results of urinalysis were within normal limits. Blood urea nitrogen was 23 mg per 100 ml. Serum electrolytes were: sodium 122, potassium 3.7, carbon dioxide 25, and chloride 89 mEq per liter. Blood cortisol at 9 a.m. was 4.6 mcg per 100 ml and at 8 p.m. was 4.8 mcg. Baseline 24-hour urine studies were as follows: 17-hydroxycorticosteroids, 0.4 mg per 24 hours, and 17-ketosteroids 2.1 mg per 24 hours.

An ACTH stimulation test was carried out for three days utilizing 25 units of ACTH in 500 ml of normal saline solution infused over an eight-hour period, and a 24-hour urine collection was completed for each day. The results: 17-hydroxycorticosteroid per 24 hours, 0.1 mg the first day, 1.2 mg the second day, and 1.4 mg the third day.

A water loading test was carried out as follows: the patient ingested 1,500 ml of water over a 45-minute period. A five-hour urine collection was then done, the patient putting out 550 ml.

An electrocardiogram showed low voltage in all leads. An x-ray film of the chest showed no evidence of pulmonary disease. The heart was noted to be remarkably small.

Thyroid studies included the following: Protein-bound iodine, 2.5 mcg per 100 ml; cholesterol, 240 mg per 100 ml; triiodothyronine, 27 percent (repeat 18 percent); tetraiodothyronine, 1.4 mcg per 100 ml (repeat 1.4); thyroid antibody, negative.

Results of glucose tolerance test (oral 100 ml glucose) was as follows: Fasting blood glucose, 82 mg per 100 ml; ½ hour 114 mg, 1 hour 146 mg, 2 hours 148 mg, 3 hours 138 mg and 4 hours 140 mg.

Skin tests were negative for tuberculin purified protein derivative intermediate, histoplasmosis, and coccidioidomycosis.

A Papanicolaou smear revealed a moderate estrogen effect.

Clinical course

After completion of baseline studies, cortisone was begun, 12.5 mg twice a day. A few days later fludrocortisone (Florinef®) 0.2 mg and sodium chloride 4.0 grams were added to the cortisone to improve the mineralocorticoid effect and replace the depleted blood volume. The patient's clinical response was slow and a loss of cortisone potency was suspected. She was switched to hydrocortisone, 10 mg three times a day. Gradually she improved with volume replacement and disappearance of postural hypotension and nausea. Her appetite increased and as her weight rose, slight edema developed. Hence, fludrocortisone was reduced to 0.1 mg daily and sodium chloride to 2 grams. She continued to improve, but at a slower rate than had been anticipated and was felt to be due to the thyroid deficiency. A month after the patient was admitted to hospital, tetraiodothyronine content had risen to 2.4 mcg per 100 ml and cholesterol had fallen to 185 mg per 100 ml, suggesting that the thyroid function was returning. A water loading test by the same method before was carried out and the five-hour urine collection was 1,200 ml. Electrolyte values had returned to normal (sodium 140, potassium 4.4, carbon dioxide 24 and chloride 104 mEq per liter). Shortly thereafter a fasting and two-hour postprandial blood glucose determination showed normal values —103 mg and 98 mg per 100 ml, respectively.

The patient's clinical status then continued to improve, with return of normal strength, disappearance of postural hypotension, clearing of persistent fatigue, increase in libido, return to previous weight, fading of brown pigmentation of the skin and increase in cold tolerance. She was able to carry on with her home, family, and full-time nursing duties. Results of thyroid function tests continued to improve. (See Table 1). A 24-hour radioactive iodine uptake and scan were

TABLE 1.—*Results of Thyroid Function Studies in Case Herein Reported*

		1969*						1970					1971
Test	*Normal Value*	11/16	11/21	11/29	12/1	12/4	12/15	1/5	1/16	1/19	3/21	9/10	6/29
PBI	3.5 to 8.0 mcg	..	..	2.8	..	..	..	..	4.8	4.6	..	..	..
T_4	3.0 to 7.3 mcg	..	1.4	..	1.4	..	2.4	3.6	3.0	..	3.9	4.0	4.9
T_3	25 to 35	..	27.0	..	18.0	..	..	28.0	29.0	..	..	29.0	..
IST_3	0.8 to 1.3	..	..	..	..	..	0.8	0.97	1.02	..	1.05	..	..
Cholesterol	150 to 260 mg	240	..	..	..	205	185	195	200	200	..	..	..

*Adrenal replacement therapy begun 11/27/69

PBI = protein-bound iodine; T_4 = tetraiodothyronine; T_3 = triiodothyronine; IST_3 = index of serum binding of T_3 (method developed at Solano Laboratories)

within normal limits. The scan was symmetrical and showed a normal sized gland.

At last report the patient's steroid dosage had been reduced slightly. She was taking hydrocortisone, 10 mg twice a day, and fludrocortisone (Florinef) 0.1 mg daily. She no longer required sodium chloride tablets, but used salt to taste with her regular diet.

Discussion

In this case the patient appeared clinically to have Addison's disease, and this was confirmed by laboratory studies. Hypothyroidism was somewhat obscured by the overwhelming signs and symptoms related to the adrenal insufficiency. The possibility of panhypopotuitarism was considered but ruled out on the basis of the presence of pronounced skin pigmentation and maintenance of menstrual periods.

Because the clinical progress was slow after adrenal replacement therapy was begun, thyroid replacement therapy was strongly considered. However, in light of the gradual apparent return of the thyroid function this was not done and in less than a year the patient's thyroid function returned to normal with only adrenal replacement therapy.

This phenomenon has been previously described by Gastineau and Arnold[1] in two cases. In one of their cases, diabetes developed as well. In the present case, the oral glucose tolerance test before treatment revealed a slow rise, with persistence of a slightly elevated blood glucose to four hours. This response probably reflected very slow gastrointestinal absorption due to her previously limited food intake and hypothyroidism, not a true diabetic state. Recently a fasting blood glucose and a two-hour post prandial blood glucose were normal. The presence of vitiligo, which preceded the endocrine problems, might suggest the development of a progression of autoimmune diathesis involving first the skin and then, later, the adrenal and the thyroid gland.

There are a number of possible explanations for reversal of this hypothyroid state associated with Addison's disease with no other treatment than adrenal replacement administration.

It is well known that in Addison's disease, lymphocytic infiltration occurs in the thyroid gland and other tissues.[3] Presumably if this infiltration is extensive enough, thyroid insufficiency might occur. However, hypothyroidism rarely does develop, suggesting that thyroid reserve is sufficient to maintain a euthyroid state in spite of compromise of the thyroid gland. Schmidt's syndrome[3] has been characterized by the occurrence of Addison's disease in association with chronic thyroiditis and atrophy of the thyroid gland, with lymphocytic infiltration of both the adrenals and the thyroid.[3] Subsequently in similar cases the patients were shown to have increased antiadrenal and antithyroid antibodies.[4] The patient in the present case did not have demonstrable thyroid antibodies. A test for adrenal antibodies was not done. The incidence of hypothyroidism and Addison's disease combined may be higher than the 2 percent discussed by Carpenter et al.[5]

Hydrocortisone replacement therapy for our patient's Addison's disease may have had a therapeutic effect on the thyroid gland through an anti-inflammatory effect on the "thyroiditis" and a reduction in the lymphoid hyperplasia and infiltration, with subsequent gradual resumption of normal thyroid activity. The replacement dose of hydrocortisone may have been adequate to suppress inflammation due to slowed metabolism and excretion of the glucocorticoid. Against this hypothesis would be the lack of history suggestive of thyroiditis, the fact that the thyroid gland was of normal size, the absence of inflammation, and the absence of thyroid antibodies.

Another theoretical explanation for this complex endocrinopathic condition could be central in nature. The anterior pituitary cells which produce ACTH and thyroid stimulating hormone (TSH) may be similar or the same.[7] There is some evidence to suggest that corticotropin may suppress TSH production.[6-8] In this patient ACTH levels, before treatment, would probably be very high due to lack of suppression by circulating cortisol. TSH levels might be extremely low due to suppression of TSH production by the ACTH, or if the cells which produce both tropic hormones are the same, production might be preoccupied with ACTH production and decreased TSH synthesis. With institution of hydrocortisone replacement therapy, ACTH production would be reduced, and TSH production would increase, with subsequent gradual "waking up" of the thyroid gland and appropriate thyroid hormone production. In a more recent report,[9] glucocorticoid administration resulted in reduction in plasma TSH concentration in both hypothyroid and normal human subjects. This observation would appear to be in conflict with the above observation. However, in the same report

it was noted that TSH rebound was observed in a high proportion of the subjects. They suggested that during glucocorticoid treatment when thyrotropin releasing factor (TRF) is presumably impaired, it could accumulate intracellularly in the appropriate hypothalamic centers. Subsequently, this accumulated TRF might be rapidly released and therefore briefly stimulate TSH secretion through its known pituitary action. Possibly in the present patient the rebound phenomenon with briefly higher than normal TSH levels resulted in adequate thyroid stimulation to resume thyroid function. TSH measurement or a TSH stimulation test would have been helpful in localizing possible sites of glucocorticoid effects on restoring the patient to a euthyroid state.

In a patient who exhibits clinical and laboratory evidence of Addison's disease and thyroid insufficiency, adrenal replacement therapy should be started and continued. The patient should be observed closely over subsequent weeks, particularly for complications of hypothyroidism; and if complications develop, gradual thyroid replacement should be initiated and maintained for two to three months. After that time the thyroid hormone could be discontinued for an appropriate period and thyroid status could be reevaluated for return of function. However if, as in the present case, the patient continues to show clinical and laboratory evidence of improved thyroid function, only adrenal replacement therapy is needed.

Summary

A case of Addison's disease associated with hypothyroidism which was corrected totally with only adrenal replacement therapy is presented. Several theoretical explanations for this phenomenon are discussed.

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Lupus Nephritis Complicated by Fatal Disseminated Coccidioidomycosis

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SYSTEMIC LUPUS ERYTHEMATOSUS, renal failure and steroid therapy are known predisposing conditions to opportunistic infectious disorders.[1-3] Among the fungal organisms causing such septic processes, Coccidioides immitis is relatively infrequent despite its classification as a "predominantly pathogenic" opportunistic fungus.[4,5] The following case report concerns a woman with end-stage lupus nephritis under treatment with corticosteroids and dialysis whose course was complicated by fulminant disseminated coccidioidomycosis. So far as we could determine, this is only the fourth patient described with lupus complicated by coccidioidomycosis[4,6,7] and the first for whom complete autopsy findings are available. A comparative description of the previous cases, the relationship to predisposing factors and the diagnostic difficulties in the current case are discussed.

Report of a Case

A 29-year-old woman was admitted to the Naval Hospital, Oakland, January 2, 1971, with uremia, hypertension and congestive heart failure. Ten years previously, while living in San Diego, the patient had had a post-partum cutaneous erup-

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tion and arthritis. A diagnosis of systemic lupus erythematosus was established with positive LE-cell preparations. Corticosteroids were prescribed and the symptoms improved. Subsequently she moved to Lemoore, California, in the San Joaquin Valley. Intermittent arthritis, photosensitive dermatitis and apparent urinary sediment abnormalities occurred which were treated with prednisone in doses ranging from 5 to 15 mg daily. Her health had been good otherwise until, eight months before admission, she noted progressive fatigue, weakness, orthopnea and generalized edema. Nausea and vomiting began a week before admission. When examined at the Naval Hospital at Lemoore, her blood pressure was 220/140 mm of mercury and there were clinical findings of congestive heart failure. The hematocrit was 25 percent. Leukocytes numbered 8,900 per cu mm with 86 percent neutrophils, 1 percent banded forms and 13 percent lymphocytes. The erythrocyte sedimentation rate was 56 mm in one hour. There was a four-plus reaction for proteinuria, and blood urea nitrogen was 130 mg per 100 ml. Results of skin tests for tuberculosis, histoplasmosis and coccidioidomycosis were negative. Therapy with prednisone, 40 mg daily, was initiated and the patient was referred to Oakland Naval Hospital. The past history was negative for pulmonary infectious disease and the patient recalled no episodes of cough, fever, chills, chest pain, cutaneous bullae or nodules. One sister had Raynaud's disease and another had arthritis.

On admission examination, the patient appeared alert but chronically and acutely ill. Blood pressure was 180/100 mm of mercury, pulse rate 120 per minute, respirations 26 per minute and temperature 37°C (98.6°F). The optic fundi were normal. Veins in the neck were distended. There was dullness to percussion at both lung bases, with decreased breath sounds. The heart was enlarged. Third and fourth heart sounds were prominent, but no murmurs were noted. The abdomen was soft without organomegaly. Mild deformity of the metacarpophalangeal joints of both hands was noted. Lower extremities were normal except for two-plus edema. The skin was pallid and there were patchy atrophic lesions with central telangiectasis in a malar distribution.

The hemacrit was 24 percent. Leukocytes numbered 6,100 per cu mm with 91 percent neutrophils and 9 percent lymphocytes. Specific gravity of the urine was 1.016, pH 6.0, protein content 300 mg per 100 ml, and there were numerous hyaline and hyalogranular casts and white cells. The blood urea nitrogen was 154 mg, serum creatinine 10.1 mg, blood sugar 154 mg, total protein 5.5 grams, albumin 2.8 grams, uric acid 8.0 mg, calcium 9.7 mg, and phosphates 7.4 mg per 100 ml; serum sodium 130 mEq, potassium 4.3 mEq, chlorides 91 mEq and bicarbonate 8.0 mEq per liter. The endogenous creatinine clearance was 5 ml per minute. Protein content of a 24-hour urine specimen was 1.8 grams. The antinuclear antibody test was positive, direct Coombs test negative and complement (B 1-C globulin) level 78 mg per 100 ml (normal 167 to 124 mg per 100 ml). Urine colony count was 100,000 organisms (Escherichia coli) per ml. An x-ray film of the chest showed diffuse cardiomegaly, pulmonary vascular congestion and bilateral pleural effusion (Figure 1). Borderline left axis deviation and nonspecific ST and T wave changes were present on an electrocardiogram. Results of repeat skin tests for tuberculosis, coccidioidomycosis and histoplasmosis were negative. Serologic studies for fungi were not performed.

Initial treatment consisted of digoxin, furosemide, hydralazine, prednisone 60 mg daily, ampicillin, fluid restriction and a low protein diet. By the fourth hospital day the congestive failure was increasing and the BUN had risen to 200 mg per 100 ml. Peritoneal dialysis was instituted and the patient's hemodynamic and metabolic status improved. On the eighth hospital day prednisone was increased to 100 mg daily. For one week after dialysis the patient felt well, was afebrile and eating well, but by the 18th day she was again having nausea and vomiting, and the BUN was 180 mg per 100 ml. Additionally she was first noted to have a temperature elevation to 37.8°C (100°F). Peritoneal dialysis was begun again, and uremia diminished. However, a low-grade fever persisted with an elevated leukocyte count—18,800 per cu mm with 97 percent neutrophils, 1 percent banded forms and 2 percent lymphocytes. A urine culture again grew E. coli and, in addition, non-hemolytic Streptococcus. Multiple blood and peritoneal fluid cultures were negative. Ampicillin therapy was resumed. On the 24th hospital day, an apparently steroid-related psychosis developed. Prednisone was reduced to 60 mg daily. Peritoneal dialysis was again started on the 28th day when the BUN rose to 195 mg per 100 ml. During dialysis the temperature increased to 38.9°C (102°F) and multinodular densities appeared in both lungs



Figure 1.—Admission chest x-ray film showing cardiomegaly, pulmonary vascular congestion and bilateral pleural effusion.

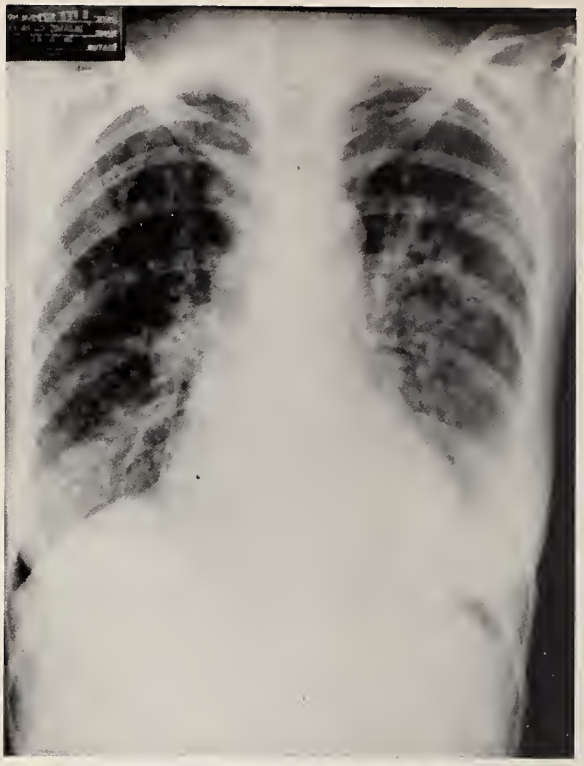


Figure 2.—X-ray film of chest demonstrating bilateral multinodular infiltrates.

(Figure 2). Sputum and trans-tracheal aspirates grew a pure culture of Enterobacter but were negative for fungi after 13 days' incubation on Sabaroud's media. In addition, a single peritoneal culture grew K. pneumoniae and Ps. aeruginosa was found in a urine specimen taken by catheter. Blood, peritoneal, urine and spinal fluid cultures were otherwise negative for fungi and bacteria. Kanamycin, followed by gentamicin, was started and the prednisone dose was reduced to 30 mg daily. Because of continued fever and an accelerated catabolic rate, hemodialysis was begun on the 30th hospital day. Dialysis was tolerated well, but fever persisted and the multinodular pulmonary densities increased. Progressive dyspnea, hypoxia, splenomegaly and elevation of the serum alkaline phosphatase developed during the subsequent two days. Despite continued antibiotic and respiratory supportive therapy, the patient had cardiorespiratory arrest and died on the 40th hospital day.

At autopsy the gastrointestinal tract, central nervous system and reproductive organs were normal. The right lung weighed 810 grams, the left lung 750 grams. The lung bases were densely adherent to the pleural surfaces of the diaphrams and there were bilateral small pleural effusions. Miliary, greyish nodules were present uniformly over both pleural and lung surfaces. There were similar nodules throughout the parenchyma of both lungs. On microscopic examination, the alveolar spaces were seen to be filled with an acute inflammatory infiltrate with foci of intra-alveolar hemorrhage and edema. Large numbers of thick-walled spherules were present on all sections, with occasional alveolar abscesses and areas of necrosis (Figure 3). Endospores were seen within intact and surrounding ruptured spherules. Fibrocaseous granulomata and Langhans-type giant cells were seen in occasional sections.

The heart weight 390 grams. The left ventricle was prominent. Scattered small abscesses containing multiple endospores were present in the left ventricular myocardium (Figure 4). The heart valves and endocardium were normal.

The liver weighed 1,900 grams. Microabscesses with spherules containing endospores were scattered diffusely throughout the parenchyma—predominantly in the periportal zones. The spleen weighed 530 grams and was almost completely replaced by abscesses. There were large coalescent bands of necrosis rimmed by neutrophils, thick-

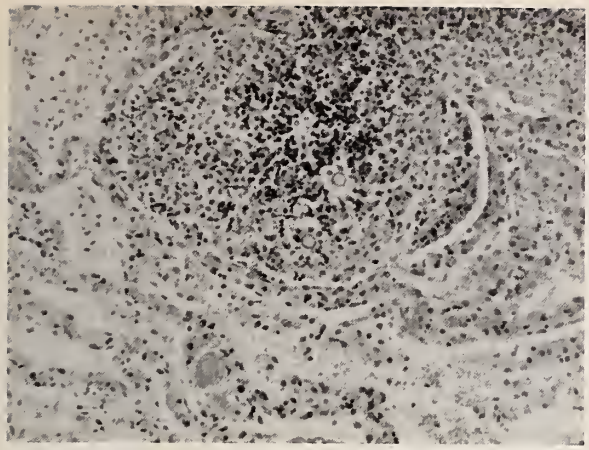


Figure 3.—Alveoli and terminal bronchiole. Note abscess formation and developing spores and spherules. (Reduced from × 100)

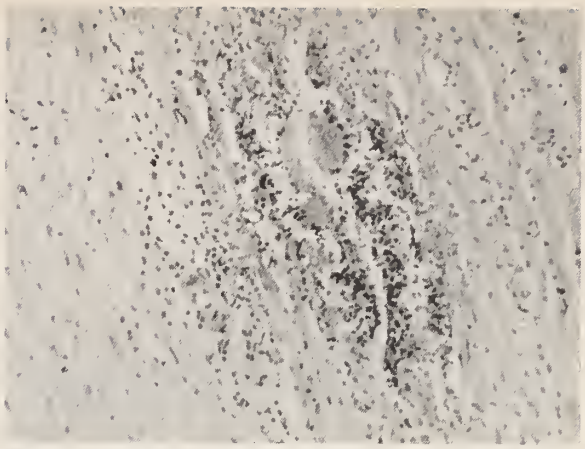


Figure 4.—Left ventricular myocardium. Numerous spores and spherules are seen within an area of abscess. (Reduced from × 100)

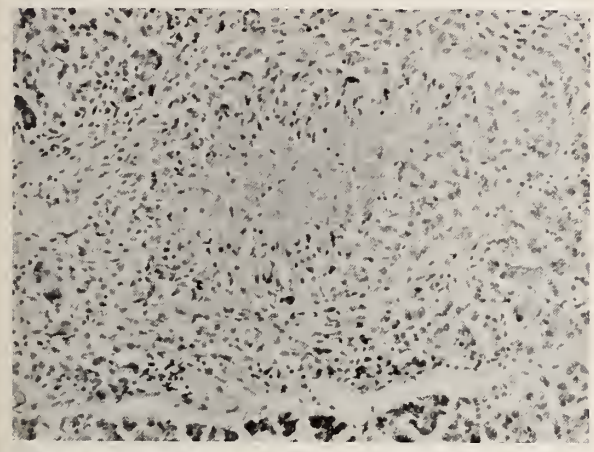


Figure 5.—Granuloma with giant cells in pancreas. (Reduced from × 100)

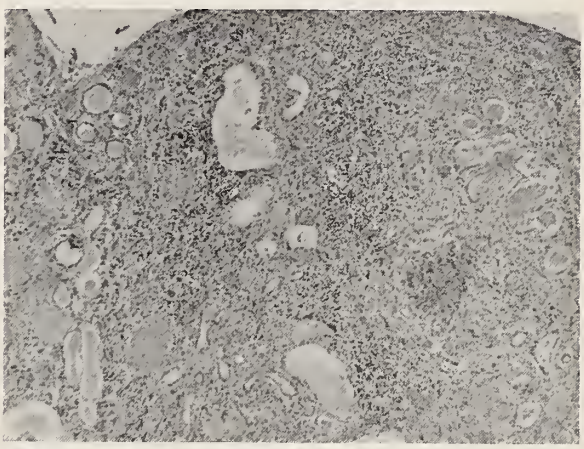


Figure 6.—Kidney section showing granuloma, hyalinized glomeruli, dilated tubules and interstitial infiltrate. (Reduced from × 40)

walled spherules and occasional giant cells. Concentric laminated fibrosis was noted around several small arteries. A single small abscess was seen in pancreatic sections (Figure 5).

Each kidney weighed 60 grams and was 8 cm in length. On microscopic examination there was diffuse interstitial fibrosis with a heavy infiltrate of lymphocytes and plasma cells in both cortex and medulla. Occasional small abscesses were found in the cortex, but microorganisms were not identified. The tubules were dilated and contained a homogenous eosinophilic material, as well as foreign-body giant cells. Medium-sized arterioles showed adventitial fibrous thickening. The glomeruli exhibited a generalized membranous pattern with focal hyalinization and obliterative changes. Fibrinoid necrosis and "wire loop" lesions were abundant. Hematoxylin bodies were not demonstrated. These changes are shown in Figure 6.

The thoracic and abdominal lymph nodes were enlarged. Those in the perihilar regions showed distortion of normal morphologic features, with replacement by abscesses, necrosis and the presence of microorganisms as described in the lungs.

Cultures of tissue from the lungs, thoracic lymph nodes, liver, spleen and kidneys readily grew C. immitis.

Discussion

In summary, the patient was a 29-year-old woman who had lived several years in an endemic area for coccidioidomycosis, and had fulminant dissemination of the fungal infection at a time when advanced renal manifestations of systemic lupus erythematosus developed while she was receiving high doses of corticosteroids. The course of coccidioidomycosis was rapidly fatal. Death oc-

curring within three weeks of the first pulmonary signs of the disease. At autopsy there was diffuse fungal infection of the lungs, liver, spleen and lymphatics, with lesser involvement of the kidneys and pancreas. A somewhat unusual finding was the sparing of the central nervous system.[8] The pathologic findings did not suggest chronic coccidioidomycosis or activation of quiescent disease. Although this possibility could not be excluded, the overall findings suggested an acute process, probably recently acquired.

Andersen and Guckian[6] reported from Texas the case of a 20-year-old Mexican-American woman with signs of systemic lupus erythematosus for a year and a half in whom fatal pulmonary coccidioidomycosis developed approximately a month after initiation of prednisone, 60 mg per day. As in the present case, the coccidioidin skin test was negative. However, the complement fixation titer was 1:16. Diagnosis was confirmed by lung biopsy, since no postmortem examination was made. A 26-year-old woman described by Berry et al[7] had been treated with low-dose steroids for 13 years for predominantly arthritic signs of lupus. Pulmonary and subsequent disseminated coccidioidomycosis occurred 18 months following the patient's move to the southwestern United States and three months after treatment was begun with 80 mg of prednisone daily plus 40 mg of ACTH daily for exacerbation of lupus symptoms. Coccidioidomycosis was controlled with amphotericin B. Coccidioidin skin and precipitin tests were negative; however, the complement fixation titer was 1:32. The other previously reported case was that of a 53-year-old man with a "drug-induced lupus syndrome who had been receiving isoniazid and para-aminosalicylic acid for pulmonary tuberculosis.[4] Progression of the pulmonary disease, with cavitation, occurred while the patient was receiving prednisone, 80 mg daily. Sputum cultures were positive for both Coccidioides and Aspergillus. Treatment with amphotericin B was followed by improvement. The coccidioidin skin test had been positive before administration of steroids was begun.

Three conditions considered to be associated with enhanced infectious susceptibility existed concurrently in the present patient—collagen-vascular disease, uremia and corticosteroid therapy. The predisposing factors in lupus are difficult to separate from those brought about by steroids, since the latter are so frequently used in that disorder. Of the granulomatous diseases, tuberculosis,[9] cryptococcosis and nocardiosis[10] appear to be most often associated with lupus. Infection, more commonly bacterial but occasionally fungal, is a well-known complication of azotemia. Among the fungal infections, cryptococcosis and candidiasis predominate.[2] The exact host defect in uremia remains obscure, but it seems to lie in the pathway of final immunologic expression rather than in depressed recognition.[11] The relationship of steroids to fungal infections is epidemiologically—and to a lesser degree experimentally—well established.[2] However, the specific occurrence of coccidioidomycosis in the presence of steroid therapy is less frequent than with other fungi. Roberts et al[4] recently reviewed this association. They reported a patient with coccidioidomycosis complicating primary biliary cirrhosis being treated with large doses of prednisone. They also found a number of cases in the literature in which coccidioidomycosis appeared shortly after steroid therapy was started. The majority of the patients also had underlying chronic lymphoproliferative malignant disease. Disseminated coccidioidomycosis has been reported in rheumatoid arthritis patients being treated with steroids;[12] however, the incidence is low. Experimentally, Newcomer et al[13] found that cortisone adversely affected the longevity of mice infected with C. immitis. Similarly, Redaelli[14] found diffuse infection of lungs and spleen in cortisone-treated rats, whereas an untreated control group manifest only occasional granulomata when injected with a Coccidioides infecting dose of like amount. They concluded that decreased connective tissue production in the steroid group predisposed to the disseminated process. Other studies have shown a pronounced depression of host cellular responses in the presence of steroid treatment.[2,15] The pathologic picture in the present case was predominantly one of microabscesses with a less obvious granulomatous pattern, which might suggest a suppressed immune responsiveness. It should be noted, however, that the pathologic features in fatal cases of coccidioidomycosis without steroids are quite variable,[8] making it difficult to extrapolate from the experimental data to the current clinical case. An additional argument against corticosteroids necessarily predisposing to severe coccidioidomycosis is the experience with the use of these agents as treatment adjuncts in cutaneous manifestations of the fungal infection. No dissemination was noted by Levan and Einstein[16] in 19 patients so treated. Dissemination is

known to be infrequent, however, in coccidioidomycosis patients with allergic phenomena such as erythema multiforme and nodosum. Despite these equivocal findings, the one feature that appears to have been common to the three previous patients and the one herein reported was the initiation of or increase of corticosteroid therapy at relatively high doses shortly before the development of clinical Coccidioides infection.

A number of diagnostic difficulties were presented by our patient. Pulmonary edema, uremic pneumonitis and "lupus" lung, as well as other nosocomial infections, were potential mimicking processes for the pulmonary manifestations. Opportunistic fungal infections had been considered strongly as a cause for the clinical picture, but numerous antemortem sputum and transtracheal specimens were negative for fungal growth. The presence of a pure culture of Enterobacter from the sputum diverted us from the more important fungal diagnosis with inadequate therapy resulting. In retrospect, a percutaneous lung biopsy should have been performed to establish the correct cause. The rather abrupt development of splenomegaly during the septic course—even though a non-specific finding—may have been an additional helpful finding in the consideration of disseminated coccidioidomycosis. Eosinophilia, occasionally of significance in active fungal disorders, was not present, an absence probably related to the steroid therapy.

The experience with this patient suggests that persons with lupus nephritis receiving corticosteroid therapy who have endemic exposure to Coccidioides are at risk of rapidly fatal coccidioidomycosis. Skin test screening is not adequate for exclusion of the disease, particularly in a patient with uremia who is receiving steroids, where attenuation of delayed hypersensitivity is common. Complement fixation studies are helpful and biopsy procedures should be undertaken to establish the cause if a septic process suggesting disseminated fungal infection develops.

Summary

A 29-year-old woman presented with end-stage renal failure due to systemic lupus erythematosus of ten years' duration. While she was being treated with corticosteroids and dialysis, rapidly fatal disseminated coccidioidomycosis developed. Autopsy revealed extensive organ system involvement with the fungal process, but with sparing of the central nervous system.

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Refer to: Meyer GW, Clark RD, Brotman M: Gastric phytobezoar and hypoglycemia. Medical management. Calif Med 118: 66-67, Feb 1973

Gastric Phytobezoar and Hypoglycemia

Medical Management

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IMPAIRED GASTRIC EMPTYING is a recognized complication of long standing diabetes mellitus.[1,2] Hypoglycemia secondary to gastric retention has been infrequently reported.[3]

Report of a Case

A 46-year-old woman with juvenile onset diabetes was admitted to hospital following a late morning hypoglycemic episode with seizure. For several months she had noted nausea, anorexia, and easy satiety. More recently, she had begun vomiting after breakfast, often recognizing undigested food from the previous night's dinner. Continuation of her long established insulin dosage resulted in late morning hypoglycemic episodes.

On questioning, the patient said she had not had diarrhea, dysphagia, numbness or paresthesiae in the extremities. Dietary history revealed that she ate large quantities of lettuce and artichokes.

On physical examination the only abnormality noted was absence of ankle reflexes.

Barium studies showed a normal esophagus and an atonic dilated stomach and duodenum with decidedly reduced gastric peristalsis. Several filling defects consistent with gastric bezoars were noted (Figure 1).

The patient was treated with a low roughage diet and papain (Adolph's meat tenderizer), one teaspoonful in juice three times daily one hour before meals. Anorexia, nausea and easy satiety improved, vomiting ceased, and diabetic control was better. Repeat barium studies after two weeks showed no evidence of retained food material (Figure 1).

Discussion

The gastrointestinal manifestations of diabetes mellitus have been reviewed.[1] Clinically significant diabetic gastroneuropathy is infrequent: it occurred in only 0.08 percent of 43,900 diabetic

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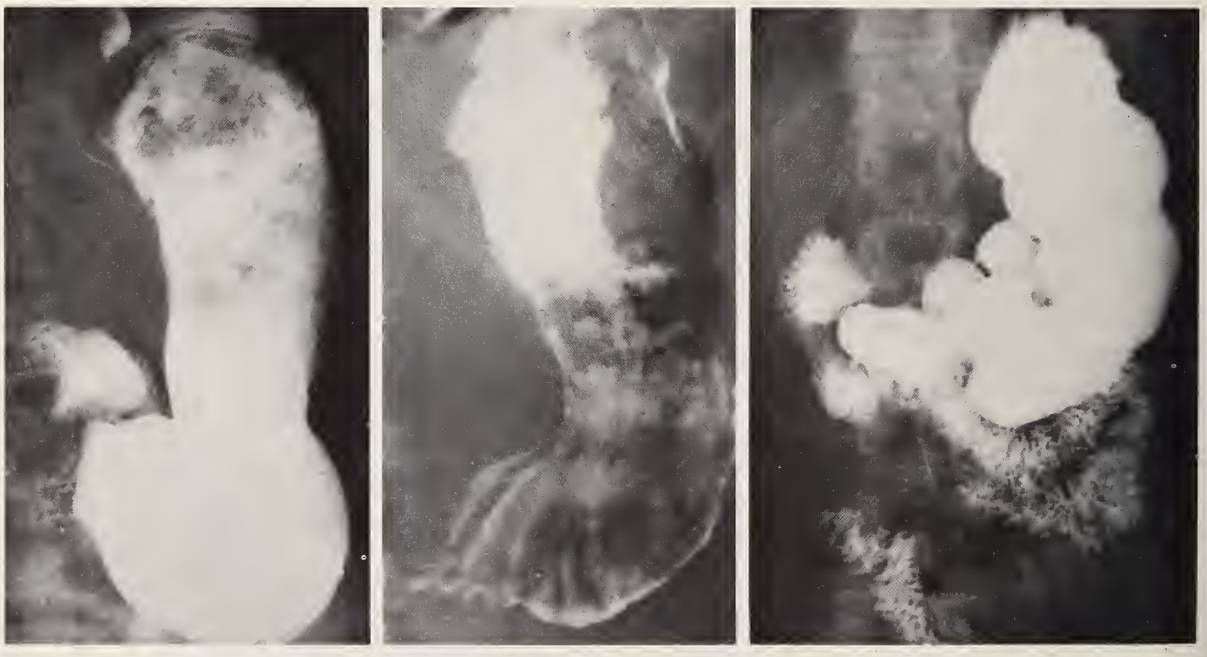


Figure 1.—Left and Center, barium study before treatment shows filling defects consistent with gastric bezoars. **Right,** after treatment the filling defects are no longer seen.

patients reviewed by Zitomer et al.[2] Most of the patients with that condition complained of vague malaise, anorexia, nausea and occasionally retention-type vomiting.[2] Rarely gastropathy will present as "brittle diabetes." In the case here presented, impaired gastric emptying and ingestion of large amounts of relatively insoluble fibre resulted in a space-occupying gastric intraluminal mass. This severely restricted the patient's dietary intake and led to post-prandial vomiting and hypoglycemia. Diabetes control was restored by treatment with papain.

Surgical operation has long been the mainstay of management of gastric bezoars.[4] However, recent reports have demonstrated successful medical management, including liquid diet for three to four weeks followed by a continuous low residue diet[4]; lavage through a nasogastric tube[5]; and apparent dissolution with papain-sodium bicarbonate,[6] cellulase[7] and acetyl cysteine.[8] Medical management of gastric phytobezoars should be attempted in all cases before surgical removal is considered.

Summary

A patient with diabetic gastropathy, phytobezoar and recurrent hypoglycemia was successfully managed with papain (Adolph's meat tenderizer).

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LETTERS *to the Editor*

Responses to "A Call for Help"

TO THE EDITOR: This is a report on the response to my letter to the Editor in the September issue [Calif Med 117:82, Sep 1972], in which I asked why our fellow-physicians are apparently so reluctant to utilize psychiatric consultation for their patients.

In all, eight physicians have replied (so far). Of the eight respondents two are in public health, two in general practice, two in surgical specialty, one in pediatrics, and one apparently retired. The eight respondents listed the following reasons for which, they believe, physicians in general are reluctant to ask for a psychiatric consultation:

1. Psychiatrists are "aloof": they (a) don't come to staff meetings; (b) don't respond to emergencies; (c) are hard to reach ("how would you like to be told to call back exactly between 2:50 and 3:00 p.m.?").

2. Psychiatrists show poor manners in consultation: (a) don't report back to the referring doctor; (b) prescribe conflicting medications without having bothered to check with the referring doctor or having taken a medication history.

3. Psychiatry is unscientific: (a) it has many esoteric theories, few solid facts; (b) psychiatrists are divided among themselves and seem more interested in promoting their respective pet theories than in objective truth.

4. Psychiatrists are not very effective: (a) they can't even help with resolving conflicts among hospital staff; (b) instead of treating the patient themselves they tend to re-refer to some intern or other mental health worker; (c) contrary to what they preach, they too "label" the patient and treat *it* (the "disease") rather than relating to him as a total human being who has problems in living; (d) psychotherapy lasts forever and its results are difficult to measure quantitatively; (e) many patients seem to get not better but worse: after therapy they become more self-deprecatory and more dependent, or else more hostile and ornery than they already had been.

5. Psychiatry still has a "stigma": (a) patients are ashamed; (b) relatives are embarrassed; (c) insurance policies don't pay!

6. Physicians' prejudice: non-psychiatrists have become conditioned to treat everything with pills and potions and have little trust in anything less tangible.

How widely these opinions prevail among physicians is, of course, an open question; one could even get defensive and argue that they are obviously biased and objectively unjustified. All I can say at this time is that *if* such opinions do indeed prevail, that would explain the observations which prompted my inquiry in the first place. It would also point up the need for much work yet to be done to bridge this apparent gap between psychiatry and other branches of medicine.

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Actinobacillus Actinomycetemcomitans

TO THE EDITOR: I read with interest the article "Bacterial Endocarditis Due to Actinobacillus Actinomycetemcomitans in a Patient with a Prosthetic Aortic Valve" by Stauffer JL and Goldman MJ in CALIFORNIA MEDICINE (Calif Med 117:59-63, Aug 1972). The authors stated that there have only been eight prior cases reported of bacterial endocarditis secondary to this microorganism. However, in August, 1971, I co-authored a paper entitled "Infection Due to Actinobacillus Actinomycetemcomitans," Meyers BR, Bottone E, Hirschman SZ, Schneierson SS, Gershengorn K which appeared in Am J Clin Path 56:204-211, 1971. In this paper we reported another case of bacterial endocarditis in a patient without prior heart disease who responded to antimicrobial therapy. We also described the microbiology of these microorganisms and their antimicrobial sensitivity, both disc and tube dilution studies. The paper also described a case of septicemia in a patient with multiple myeloma.

This article is brought to your attention because we feel that the antimicrobial sensitivity studies may be helpful in future therapy of these microorganisms and to emphasize that an adept bacteriology laboratory is necessary to isolate and characterize these bacteria.

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A Question of Significance

To the Editor: Dr. Henry Bourne's lucid discussion of the University Group Diabetes Program study (Tolbutamide—Therapeutic trials and clinical practice—Medical Staff Conference, University of California, San Francisco, California Medicine 117:45-62, December, 1972) should be very helpful to the clinician in deciding how to treat a diabetic patient. His analysis complements Feinstein's statistical "inquest"[1] and should leave little room for further controversy until a really definitive therapeutic trial can be undertaken.

Dr. Bourne, however, makes one point where I think the emphasis is misplaced. Looking at the comparison between the placebo and insulin variable groups, he takes the small mortality difference observed (10.2 percent in the placebo group and 8.8 percent in the insulin treated patients) as evidence that insulin has had no effect. Surely this puts too much of a burden on the finding of a difference which is not statistically significant. Suppose, for instance, that the true mortality in the placebo population is 12 percent and in the insulin treated population 6 percent; if we draw repeated samples of 204 or 205 from these two groups we would expect to find differences as small as were observed in the study (or smaller) in slightly over 5 percent of our experiments. Consequently, there could very well be a real and important difference in patients treated with insulin. A verdict of statistical non-significance only means that a difference has not been demonstrated —it does not prove that no difference exists.

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Meaning of Dysmature

To the Editor: My reply to Dr. Szalay's letter (Calif Med 118:41, Jan 1973) is as follows:

Dr. Szalay is quite correct that much confusion does exist not only in regard to terms but also to concepts. Simplification is indicated. The proliferation of terms and categorizations has tended in the past to perpetrate much nonsense and to obscure the fact that these small babies from abnormal pregnancies can be conceptualized more easily as a unit and categorized rather handily as we have tried to do. The stimulus for this classification actually comes from the first report of the British Perinatal Mortality Survey[1] from which the following is quoted: "Dysmature is a term with no agreed on precise definition, which is here used not as a clinical description of an infant but only to apply to those babies that are *abnormally small or large by weight* for the duration of gestation when this is accurately known." Clifford's "placental dysfunction syndrome"[2] refers to babies that are truly postmature—a limited syndrome.

If one identifies a dysmature baby, he then can consider a classification and/or cause—maternal, placental, genetic, metabolic, infectious, etc. The fact that a baby with a 17-18 trisomy for example is small for gestational age is best understood, it seems to me, if we regard him as a dysmature infant due to chromosomal aberration. My bias is clear, that in a confusing area where author after author sought to introduce a new term for the same thing, we would do well to recognize them as fetal growth failures or excesses and then to categorize them according to cause. Otherwise, in addition to Dr. Szalay's "descriptive phrases" we would also be forced to add "fetal malnutrition,"[3] "chronic fetal distress,"[4] "placental insufficiency syndrome,"[5] and "runt."[6]

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Refer to: Veith I: Acupuncture in traditional Chinese Medicine—An historical review. Calif Med 118:70-79, Feb 1973

SPECIAL ARTICLE

Acupuncture in Traditional Chinese Medicine

—An Historical Review

ILZA VEITH, PhD, *San Francisco*

WITH THE RESUMPTION of political, diplomatic, scientific, and cultural relations between the United States and China a veritable epidemic of interest has developed in America in the seemingly most bizarre aspect of Chinese medicine. It appears that recent American visitors to China believed they had "discovered" acupuncture as though it were an entirely new phenomenon in the long history of Chinese medicine.

Indeed the American visitors, no matter whether they were diplomats, "China scholars," ping-pong players, or even physicians, were so overwhelmed by the dramatic use of acupuncture anesthesia in major surgical operations that they failed to realize that this was the only *new* aspect of acupuncture, whereas, in fact, the practice of needling dates back at least seven thousand years to neolithic times when the first needles were made of stone.

Thus acupuncture is only a part of a rich, intricate, and ancient medical system which must be appreciated in its totality in order to yield an explanation for the phenomena that were observed by the recent American visitors.

The origins of China's medical history are veiled in legend. Tradition ascribes the oldest Chinese medical work, the *Huang Ti Nei Ching Su Wen "The Yellow Emperor's Classic of Internal Medicine,"* to the authorship of Huang Ti, the Yellow Emperor, whose life span is said to have extended from 2697 to 2597 B.C. While it is not possible to state with any certainty when this great work was actually written down, a number of textual references and many touches of Taoist thinking point to the fourth or third century B.C. The form in which *The Yellow Emperor's Classic of Internal Medicine* has come down to us was given to it in 762 A.D. by Wang Pin of the Tang dynasty, the ablest and most vigorous of the many scholars who interpreted, commented upon, and elaborated this fundamental book, which is even now the basis of Chinese medicine.

It is significant in many ways that the work should have been attributed to an emperor whose reign was so early in the nation's history. Even at the time when it was first conceived, the *Classic* was obviously destined to be of lasting value, and its actual author, or authors, sacrificed the desire for personal glory to the supreme task of creating a work for eternity. This could best be done by ascribing the authorship to an exalted and ancient being, for China's reverence of antiquity dates back to its earliest days.

The naming of one of the ancients as an author was not without some justification, since the wording of the work makes it evident that its contents had been the intellectual property of the Chinese for a very long time before they were formulated and put down. The traditional dates of Huang Ti, the Yellow Emperor, make him a perfect choice for the hypothetical author of a work that stresses

Based upon the introductory lecture given at a Symposium on "Traditional Chinese Medicine Today" held on October 27, 1972 at the University of California, San Francisco.

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health and long life. He himself is supposed to have lived for one entire century, and this, according to the *Classic*, is the ideal span of life. But there is another, and perhaps the most interesting, purpose which can be inferred from the text of the *Yellow Emperor's Classic of Internal Medicine*, and even more from the form of the text itself: The work is written in the form of a dialogue between Huang Ti and his Prime Minister Ch'i Po, in which the Emperor—often in the humblest way—seeks instruction in all questions pertaining to health and the art of healing.

Although this conversation can hardly be considered an historical fact, the involvement of the names of these two distinguished personages is strongly indicative of the exalted place accorded to medicine in ancient China. It seems certain that the authors of the *Classic* considered knowledge of the forces that cause life and death worthy of an emperor and the art of healing to be the predominant responsibility of the elect. The grave obligation imposed by the mastery of the healing art finds expression in the Emperor's solemn vow: "I shall smear my mouth with blood and take an oath that I will not venture to receive this information were I to use it recklessly or neglect it."

Beyond doubt, the practice of medicine has often been connected with an awareness of the moral responsibilities of the practitioner, and the wording of the Yellow Emperor's vow brings to mind the Hippocratic Oath. But the *Huang Ti Nei Ching Su Wen* differs from the Hippocratic writings which form the basis of Western medicine. The latter were written to give practical advice to the practicing physician; the former goes far beyond the scope of a medical textbook, being a treatise on life itself.

In the modern mind, medicine is regarded as perhaps the most highly developed of all natural sciences. Religion, philosophy, thoughts on cosmogony and the course of the universe hardly influence the actions of the present-day physician; ethics is a professional guide that helps the doctor guard himself from professional mistakes, and perhaps against malpractice suits, but the patient's ethics, except in so far as it may influence his psychological well-being, is of no concern to the physician.

The immense difference in the ancient Chinese concept of the art of healing can best be illustrated by a short passage from the *Classic:*

> [The Yellow Emperor said] "I urge you to bring into harmony for me nature, Heaven, and Tao [the right way]. There must be an end and a beginning. Heaven must be in accord with the lights of the sky, the celestial bodies, and their course and periods. The earth below must reflect the four seasons, the five elements, that which is precious and that which is lowly and without value—one as well as the other. Is it not that in Winter man responds to Yin [the principle of darkness and cold]? And is it not in Summer he responds to Yang [the principle of light and warmth]? Let me be informed about their workings."
>
> Ch'i Po replied: "Truly a subtle question! It demands that one decypher Nature to the utmost degree."
>
> The Emperor exclaimed: "I should like to be informed about Nature to the utmost degree and include (information) about man, his physical form, his blood, his breath of life, his flowing and his dissolution; and I should like to know what causes his death and his life and what we can do about all this."

Here we see the essence of early Chinese medical thinking. A medical science did not exist by itself; the art of healing was part of philosophy and religion, both of which propounded oneness with nature and the universe.

The Yellow Emperor's Classic was written long after theories of cosmogony and the workings of the universe had been conceived and become formalized. The work does not contain basic explanations of phenomena, since the reader was expected to be familiar with the most important concepts of philosophy and religion. Before these concepts are explained here, it must be stated that there was little or no distinction between religious and philosophical thought in ancient China. Nor does the word religion in this context refer to any of the three major cults: Confucianism, Taoism and Buddhism. To be sure, certain elements of Confucian and Taoist doctrine can be found in the philosophic-religious thought of the *Classic*, but they are representative of the earlier writings rather than of the later, formalized cults.

In the passage of the *Classic* quoted above, mention is made of the three essential features which form the basis of all reasoning underlying Chinese Universalism in general, the *Huang Ti Nei Ching Su Wen* in particular, and finally Chinese medical thinking in its entirety. These three features are

the *Tao*, the *Yin* and the *Yang*, and the five elements mentioned in the dialogue are water, fire, wood, metal and earth, all of which have their place and function in the Chinese concept of the creation of the world. Since Chinese traditional thinking conceives of man as composed of the same elements as the universe and as functioning along the same principles as the macrocosm, it might be well here to summarize briefly the Chinese concept of cosmogony.

That this concept was the result of philosophical rather than religious thinking becomes immediately evident when one realizes that creation was never attributed to a superior or superhuman being. It was thought that the world had created itself, driven by Tao, an abstract motivator, which remained active and turned into a moral guide, once creation was accomplished. It was Tao, the Way, that caused the original state of chaos to divide into two forces, known as the Yin and the Yang, the female and the male, the negative and the positive elements. Even after creation was completed, Tao remained effective in guiding the functions of everything within the universe, while Yin and Yang in their ebb and flow of opposition and attraction to each other maintained all things and beings of the newly created world in their proper balance and harmony.

During creation, the Yin and the Yang brought forth the five elements: water, fire, wood, metal and earth. These formed the material substance for everything in this world. The correct proportion of these elements was preserved by the workings of the Tao and the interaction of the Yin and Yang.

In the macrocosm the visible results of perfect balance were the change from day to night, the rising and the setting of the sun, the waxing and the waning of the moon, the unchangeable sequence of the seasons, the planting and the growing of the crops. Droughts and floods, failure of the crops, and other natural phenomena were indications of a disturbance in the balance of nature.

Man, who was created with the universe and in its image, owed his health and hence his life, to the harmony of natural forces; if this harmony was upset, the result was disease and death. But while the macrocosm of the universe was left to the course of Tao and the natural forces, it was up to man to shape his fate by compliance with Tao, the Way, and thus to keep the proper balance of Yin and Yang, the two opposing forces.

The Yellow Emperor's Classic is the first book that explains to man what he can expect by living according to the Tao and thus according to nature, and how he can learn to adapt his life to this system:

> Just as the breath of the blue sky [is calm], so the will and the heart of those who are pure will be in peace, and the breath of Yang will be stable in those who keep themselves in harmony with nature. Even if there are noxious spirits they cannot cause injury to those who follow the laws of the seasons.

But the book also stresses the effects of disobedience to the Tao, the resulting disease and premature deterioration:

> Those who fail to preserve this [good conduct] will have their nine orifices closed from the inside, and the development of their muscles and flesh will be obstructed from the outside, and the breath of protection will be lost to them. This then is called: "to injure one's own body and to destroy one's own force of life."

The preceding quotations are evidence that the *Classic* was directed to the educated layman as well as to the physician, but for the latter it has much specific advice which reaches its highest wisdom in the following exhortation:

> . . . the sages did not treat those who were already ill; they instructed those who were not yet ill. They did not want to rule those who were already rebellious; they guided those who were not yet rebellious. To administer medicine to diseases which have already developed and to suppress revolts which have already developed is comparable to the behaviour of those persons who begin to dig a well after they have become thirsty, and of those who begin to cast weapons after they have already engaged in battle. Would these actions not be too late?

It is easy to see why the Chinese conceived a naturalistic philosophy and clung to it for thousands of years. They have been and still are to a large extent an agricultural people, totally dependent upon nature's immutable course. Thus it was natural for them to think of themselves as one with the universe which provided them so directly

with their livelihood. Because of this it was possible for the theories of *The Yellow Emperor's Classic* to become the basis of all subsequent medical writings and to survive up to the present day.

One may wonder how this transfer of the concepts of the macrocosm to the body of the human being was brought about. First of all, it must be said that this could have taken place only in a society that venerated the ancestor—and hence the dead—, that considered the study of anatomy a desecration of the dead, and the performance of surgery a permanent disfigurement and an infringement upon the sacredness of the body. In such an atmosphere of thought, the human structure and the physiological processes could not be investigated; they had to be taken for granted. It will be realized that under these conditions it was possible to explain human anatomy and physiology by an analogy to the universe and in terms of the theories of Tao, Yin and Yang, and the five elements. The following discussion will reveal that such analogies were not carried out altogether arbitrarily, and that occasional flashes of insight and wisdom went into their making.

In accord with the prevailing taboos, *The Yellow Emperor's Classic* and most succeeding Chinese medical works restricted their anatomical investigation to a vague study of surface anatomy. Thus it was said that the exterior of the body consisted of skin, flesh, muscles, tendons and bones. In addition there were nine orifices, provided by the eyes, the ears, the nose, the mouth, the anus, and the urethral openings. The description of internal structure and organs was as follows: Man was composed of "intestines," the five *Tsang*, or storing organs, and the six *Fu*, or eliminating organs. The five *Tsang*, which were held to be more important than the eliminating organs, were the liver, the heart, the spleen, the lungs, the kidneys. The six *Fu* were the stomach, the large intestine, the small intestine, the urinary bladder, the gall bladder, and the "three burning spaces"—an imaginary organ, whose three components were held to be distributed over the upper, middle and lower parts of the body. The storing and eliminating organs were connected by a system of vessels of which there were two kinds: those which carried blood and those which carried air or a vital pneuma. The latter have since become known as *meridians*.

This is a bare outline of the existing anatomical descriptions, but it may be sufficient to establish a parallel with the components of the universe and to form a basis for theories on the functions of the organs. In the *Classic*, the Yellow Emperor is quoted as saying:

> "Covered by Heaven and supported by Earth, all creation together in its most complete perfection is planned for the greatest achievement: Man. Man lives on the breath of Heaven and Earth and he achieves perfection through the laws of the four seasons."

The analogy between the human being and the four seasons was fortified by a preconceived numerical concept of the components of man: thus the body was believed to consist of 365 individual parts, obviously corresponding with the 365 days of the year; the number of main vessels or meridians that carried blood and air was 12 pairs and thus conformed with the 12 months; and lastly there were the *Tsang*, the five main organs representing the five elements.

Physiology, like anatomy, was based on the theories governing the creation of the world. The functioning of the body depended upon the two forces that created the world and men, the Yin and the Yang. While Yang, the male or positive principle predominated in man, and Yin, the female or negative principle, predominated in woman, neither of these forces ever existed alone, but a certain proportion of both had to be present in every well-functioning human being. These two ever-active forces, alternately opposing and supplementing each other, were held to exist within all parts of the body and to circulate through the vessels that carried blood and pneuma. Pathological conditions arose out of abundance of either the Yin or the Yang, obstruction of the flow of blood and especially the pneuma. All these deficiencies and obstructions disturbed the balance of the organism as a whole, but usually affected one particular organ.

The concept of a disease entity as it is known to modern medicine did not exist in traditional Chinese thought. Some specific fevers were known and even distinguished according to a vague groping toward a knowledge of etiology, but even the possible causes of disease were subordinated to the general scheme of the universe. Thus, the five atmospheric conditions — wind, heat, humidity,

dryness and cold — closely related to the five elements, could bring about such diseases as "injuries of the cold" (this group included typhoid fever), "injuries of the heat," "the wind within," and "humid warmth." Smallpox, leprosy and various forms of intermittent fevers were also believed to arise out of atmospheric conditions. But it was generally believed that whatever immediate cause was held to be responsible for a particular disease, the patient had laid himself open to such an attack by a major infringement of Tao, the Way, and the invariable result was a disturbance of the balance of Yin and Yang.

It is noteworthy that *The Yellow Emperor's Classic* does not present these doctrines in flat statements, but that they are clothed in symbolic imagery which compares the functioning of the body to that of a state. The relations of the various organs to each other are likened to those of the high officials, and all are dependent upon the heart, which is described as "the minister of the monarch who excels through insight and understanding." It may well be that the following paragraphs were meant to carry a political as well as a medical message, although the text is presumably concerned with the body:

> When the monarch is intelligent and enlightened, there is peace and contentment among his subjects; they can thus beget offspring, and bring up their children, earn a living and lead a long and happy life.
>
> But when the monarch is not intelligent and enlightened, the twelve officials [the organs of the body] become dangerous and perilous; the use of Tao [the Right Way], is obstructed and blocked, and Tao no longer circulates warnings against physical excesses.
>
> Afflicted are those who dissipate; they become nervous and startled. But those who are aware of their needs and desires are encouraged, and as an expression of this encouragement they become peace-loving and virtuous.

By means of these seemingly abstract theories, the ancient Chinese arrived at two extremely important conclusions: first, that disease is rarely localized, but generally affects the entire human being; and, second, that disease is often associated with behavior and with a feeling of guilt, derived from the infringement of a moral law. *The Yellow Emperor's Classic* abounds in statements concerning the effect of emotional states on health which can truly be termed precursors of psychosomatic medicine. It might be well here to quote some of the most pertinent ones:

> The Yellow Emperor said: "Man's place of residence, his motion and rest [his circumstances of life], his courage and cowardice—do they not also cause change within the vascular system [pulse]?"
>
> Ch'i Po answered: "Yes, in general, man's fear and apprehension, his passion [anger] and his suffering, his motion and his rest, they all cause changes.
>
> "Therefore it is said: In order to examine the course of a disease one must investigate whether man is courageous or nervous and cowardly, and one must examine his bones, flesh, and skin and then one can know the facts which are necessary for the methods of treatment."

From the preceding discussion it is not to be wondered at that even the infringements of the laws of behavior were systematized to the point of absurdity, as may be seen in the following sentences:

> Those whose demeanor is dissolute and licentious get a disease of the lungs. Those who are lazy and full of apprehension and fear, have difficulties in breathing, emanating from the lungs. Those whose demeanor is immoral and dissolute will injure their hearts.
>
> Thus in Spring and in Fall, in Winter and in Summer, during the four seasons and during the periods of Yin and Yang, diseases are created, that are caused by faulty practices and transgressions which have become habit.

But even these schematizations do not detract from the basic wisdom which realized the existence of a strong bond between the human body and the mind. With such principles in mind the ancient Chinese physician functioned not only as a healer of disease, but even more as a moral guide who helped his patients to acknowledge and rectify their infringements of moral and natural laws. Being a judge of man's behavior as well as of his health presupposed a high moral and ethical attitude on the part of the early Chinese physician and a fairly well-organized state of the medical profession. And indeed, in the *Chou Li*, the "Rites of the Chou," whose dynasty flourished between 1122 and 221 B.C., we find the outlines of a medical organization with a well-defined hierarchy graded according to achievement and therapeutic success.

It is clear that neither the knowledge of a disease as affecting the entire human being, nor the realization of a psychic factor as a cause, absolved the Chinese doctor of making a diagnosis of the nature and location of any particular illness. It is in the field of diagnosis that we find the least trace of realism and the greatest amount of schematization.

The main diagnostic method employed by the Chinese physician of antiquity, and still that of the traditional Chinese physician of today, is the taking of the pulse. This means of diagnosis is so intricate that it required several chapters in *The Yellow Emperor's Classic*, which were elaborated and expanded by Wang Shu-ho (about 280 A.D.) into a separate treatise of ten volumes, entirely given over to the study of the pulse. The importance attributed throughout the centuries to pulse diagnosis can be gauged by the fact that from the time of Wang Shu-ho until today at least 156 additional books have appeared on the subject.[1] The instructions concerning the pulse contained in *The Yellow Emperor's Classic* are briefly summarized here.

The pulse, it was said, consisted of six pulses on each wrist, each connected with a particular organ of the body, and each able to record even the minutest pathological changes taking place within the body. The procedure of palpation differed according to the sex of the patient; the physician first examined the pulses of the right wrist of female patients and those of the left wrist of male patients. By means of the pulse the physician was supposed to be able to judge the site and the state of the disease, its cause and duration, whether it was chronic or acute, and whether the patient would recover or die. When we realize that the seasons, the time of day, weather conditions, and the age of the patient were held to cause differences in the sounds of the pulse beats, we become aware of the immense difficulties confronting the Chinese physician. And yet, their diagnoses were surprisingly accurate. Dr. Edward H. Hume, who was present at a number of such examinations, tells us that "many visits to patients in company with proficient Chinese physicians of the old school have shown . . . how almost uncanny is their power of recognition of organic conditions through pulse observation alone."[2] Dr. Hume's statement finds corroboration from many other Western physicians who were astounded by the same phenomenon. A few selections from *The Yellow Emperor's Classic* may serve to illustrate the preceding discussions:

> The way of medical treatment is to be consistent. It should be executed at dawn when the breath of Yin has not yet begun to stir and when the breath of Yang has not yet begun to diffuse; when food and drink have not yet been taken . . . when vigour and energy are not yet disturbed — at that particular time one should examine what has happened to the pulse.
>
> If it were not for the excellent technique and the subtlety of the pulse one would not be able to examine it. But examination must be done according to plan and the system of Yin and Yang serve as basis for examination. When this basis is established, one can investigate the twelve main vessels and the five elements that generate life. Life itself follows a pattern that was set by the four seasons.
>
> Those warm and genial days of Spring lead up to heat of Summer, and the anger one might feel in Autumn makes way for forgiveness and mercy which one feels in Winter. This change of the four seasons influences the upper and lower pulses.

Diagnosis of the pulse was supplemented by a study of the patient's complexion, the changes of which were held to be indicative of the future development of the disease. The examination of the colors of the various parts of the body was carried out according to a fixed system of correlations between colors and "intestines" rather than according to actually observable phenomena. The ancient Chinese physician also interrogated the patient and his family and — interestingly enough—interpreted the patient's dreams in relation to his illness.

A study of therapy as advocated in the *Classic* indicates the ever-present preoccupation with the laws of the universe:

> In order to effect a cure and relief, one must not err towards the laws of Heaven, nor towards those of the Earth, for they form a unit.

Accordingly, the physician was told that the five elements were paralleled by five methods of treatment. Since, however, disease was not a natural phenomenon—the earliest and wisest inhabitants of the earth were reputed to have been entirely free from it because of their virtuous mode of life—these five methods were not developed simultaneously; they evolved successively

with the increasing lawlessness of succeeding generations.

The *Classic* reports that the first method of treatment evolved by the Chinese was the cure of the spirit. This method, strangely reminiscent of the most modern medical theories, consisted in helping the patient find the right way of life, that is, in finding contentment, repose and in avoiding excesses and ambition: "Those who are satisfied with their station in life will rise above it."

The second method of treatment was the nourishment of the body. To do this correctly, the physician had to consult the five elements and the various factors related to them. The *Classic* states that "each of the diseases of the four seasons and the five main organs reacts to that one of the five flavours to which (each of the seasons and the the organs) responds." The five flavors—sour, bitter, sweet, pungent and salty—were held to be related in this order to the liver, the heart, the spleen, the lungs and the kidneys, and were supposed to have in this connection a binding, strengthening, retarding, dispersing and softening effect upon the intestines. This rather rigid scheme of concordances of the five flavors was softened by the statement that in general the produce of each season and each particular region constituted the ideal nourishment.

The next method of treatment advocated in the *Classic* concerns the true effects of medicine. Here again we are referred to the five predominant qualities contained in each of them; but the subject is treated too generally to repay detailed study. Beyond the mention of the existence of medicines, which were derived from the animal, vegetable, and mineral kingdoms and held to represent a mixture of Heaven and Earth, we do not find an elaboration of the matter.

The Yellow Emperor's Classic, like most other later works dealing with internal medicine, does not contain much pharmacological information, which is reserved for the numerous treatises specifically devoted to the description of China's famous materia medica. The earliest of these *Pen Tsao* or "Herbal" was attributed to the authorship of Shen Nung, the "Divine Husbandman," another of China's legendary emperors.

The fourth method instructs the physician on how to combat disorder of the bowels and the viscera; this was done mainly by massage and by insistence upon proper evacuation of the bowels and elimination of the waters.

The methods of treatment so far discussed presuppose an attitude of watchful waiting on the part of the physician. The guidance towards proper conduct, the establishment of a correct diet, the designation of a few medicines and the insistence upon daily evacuation appear to us as an encouragement of the healing power of nature rather than as active means of curing disease. It is the fifth method of treatment, however, that enables the physician to take an active part in combating illness; and, since this method represents the most important expression of universalistic philosophy as applied to actual medical practice, I should like here to devote some time to its description. This method is the application of acupuncture and moxibustion.

Acupuncture

Acupuncture, also known as "needling," consists in the insertion of needles of various shapes, sizes and materials into specific points of the body, the extremities and even the head. The word *acupuncture* is derived from the Latin *acus* (pointed or sharp) and *punctura* (puncture) and thus means the puncturing of bodily tissue with sharp needles. These needles may be withdrawn immediately, left *in situ* for some time, or rotated a number of times, depending on the nature of the ailment. Moxibustion, or moxa treatment, is practiced by applying to the skin combustible cones of the dried and powdered leaves of Artemisia vulgaris; these cones are then ignited and allowed to burn down to the skin until a small blister forms.

The word *moxibustion* is a contraction of *moxa* and *combustion*. Moxa is derived from the Japanese expression *mogusa*, which means "burning herb." Moxibustion was enthusiastically received in Japan where it is still practiced in its original form as an alternative or supplement to acupuncture, regardless of the burn scars that have resulted. In China, on the other hand, moxibustion has continued in a somewhat attenuated form. Instead of bringing the burning moxa stick so close to the skin that a blister results, the moxa has gradually been removed from the skin, and is now used almost exclusively for the heating of the needles or the warming of the acupuncture points from a distance.

Both remedies are of great antiquity and must have been well known as early as the time of the composition of *The Yellow Emperor's Classic*, for the book deals with refinements of procedure, rather than with basic instructions concerning

their use. The cosmological significance of both these methods of treatment lies in the location and number of acupuncture and moxibustion spots, and in the motivation given to their use.

In order to understand the theories behind acupuncture and moxibustion we must bring to mind again the basic concepts of pathology and physiology as discussed above. Disease was believed to arise out of an imbalance of the dual force Yin and Yang, leading to an obstruction of *Ch'i* the vital essence, within the 12 pairs of main vessels which were held to be connected with the various parts of organs of the body. Significantly, there are 365 points where these vessels rise to the surface of the body and thus present the spots for acupuncture and moxibustion. From among these the modern Chinese acupuncturists have selected those that have proved to be most efficacious. The effect of the insertion of the needles and the blistering of the moxa cone is to create openings for the relief of congestion of *Ch'i*, caused by a plethora of Yin or Yang. According to the *Classic*, acupuncture and moxibustion were applied for a vast variety of complaints, and especially for acute pains produced by rheumatism, gout and neuralgic conditions, abdominal cramps and colics; both were recommended in cases of mental disturbance:

> Ch'i Po said: "In order to puncture one must enter the meridian repeatedly, and one uses the moment of inhalation to push the needle. Hence, in order to nourish and care for the spirit and mind one must be aware of the appearance of the body: whether it is fat or thin, whether the blood, the vital essences, the constitution and the breath are flourishing or deteriorating."
>
> The Emperor said: "How wonderful this reasoning! To bring into agreement man's body with Yin and Yang, the two principles in nature, and with the four seasons; his echoing of want and fullness, his response to the most subtle influences. . . ."

The description of these various methods of therapy concludes the discussion of the fundamentals of Chinese medicine. But these fundamentals, conceived in the dawn of China's existence and recorded centuries before our era, have not been relegated to the realm of history. In spite of the advent of Western practices, the Chinese have never completely ceased to employ their own art of healing, mainly because it continued to fit into their specific philosophy of life, but also because it appeared that in frequent cases it was good medicine. Even though many Chinese doctors and patients of more recent centuries may no longer have been consciously aware of the cosmological basis of their treatments, works like *The Yellow Emperor's Classic* and the many that followed provided such detailed methods of procedure that individual reasoning was unnecessary.

The thought of man's origin and composition as part of the universe never, however, quite left the Chinese mind and was the only existing theory until the introduction by Western scientists of the study of anatomy and the practice of surgery. Even in Japan, where Chinese medicine was adopted in the sixth century A.D. and retained until well into the sixteenth, there can be found a deep-rooted and unquestioning belief in the analogy between man and the universe.

If the ancient theoretical foundations were kept alive, it is even less surprising that the methods of treatment are still practiced in China and Japan. The examination of the pulse has remained the main diagnostic method of the traditional Chinese and Japanese practitioner. And, while the materia medica has become richer and more varied than had been described in *The Yellow Emperor's Classic*, it is still applied according to the same principles. Acupuncture and moxibustion, too, have remained in uninterrupted use. A Chinese treatise, the *Ming T'ang Ching* (probably composed during the Sung dynasty, 960-1279 A.D.), translated into Japanese as the *Mei-do-kiyo,* elaborated on the instructions given in *The Yellow Emperor's Classic*. The most graphic description of these practices from a Western point of view is contained in *The History of Japan . . .* 1690-92 by Engelbert Kaempfer, a German physician who was attached to the Dutch settlement in Deshima in the late 17th century.

For the past decades the preoccupation with ancient Chinese medical methods no longer seems to be the exclusive domain of the indigenous practitioner. Articles, books and numerous personal communications bring to light the fact that physicians all over Europe long ago began scientific investigations into the actual value of these methods which have remained in practice for more than five thousand years.

The New Interest in Acupuncture

Suddenly in 1972, the flurry of interest in the United States in the practice of acupuncture has induced innumerable desperately ill patients to seek this apparent cure-all, and, what is more important, the medical profession of this country has begun to evince a strong interest in the methods and scientific basis for the success of acupuncture therapy and surgical analgesia.

In all probability none of the often-mentioned theories on the neurophysiological mechanism of acupuncture is the last word in the explanation of the needling therapy, and it is entirely uncertain whether it will eventually be one or several investigators in the People's Republic of China or American researchers who will succeed in finding the one valid scientific basis for this mysterious operation which so far has eluded them. The immediate and perhaps somewhat simplistic response of many American physicians who are not themselves familiar with acupuncture has often been that it can simply be equated with hypnosis, that is, suggestion. That this "explanation" can hardly be considered the correct one is evident from the fact that acupuncture is effective in the treatment and relief of pain of infants in the first few months of their lives, and also of a great variety of animals. Neither infants nor animals have as yet been known to be hypnotisable.

If the history of *The Yellow Emperor's Classic* is compared with that of the *Corpus Hippocraticum*, which originated at about the same time, a curious and somewhat contradictory development may be noted. The works of the Greek tradition were composed to serve as textbooks for the practitioner, yet the practical value of their contents was superseded centuries ago. Apart from their significance for the medical historian, the value of these works has for centuries consisted in creating for the Western physician the moral and ethical concept of the ideal physician. On the other hand, from the preceding discussion it should be evident that China's earliest book concerned with the art of healing was never meant to be a mere textbook of medicine, but rather a treatise on the philosophy of nature; and yet it was taken over by physicians, not as a guide towards an ideal of life, but as a help for the actual practice of medicine. It is not within the scope of this paper to make further comparison between the literary monuments of two such divergent traditions, but it is hoped that the modern doctor, whose spiritual ancestor is Hippocrates, and who today is trained in clinical research and the psychosomatic aspect of disease, will not fail to discover the philosophical wisdom of *The Yellow Emperor's Classic of Internal Medicine.*

Speculation on the Success of Acupuncture

Since Western medicine cannot but speculate about the scientific secret of acupuncture, several theories have been suggested that might account for the uncanny success of the oriental procedure. Here we must draw on the work of men of such scientific sophistication as Rasmussen and Penfield who showed exactly 25 years ago that each area of the surface of the skin is represented by a corresponding area in the cerebral cortex. (Rasmussen, T. and Penfield, Wilder: "Further Studies of the Sensory and Motor Cerebral Cortex of Man." *Federation Proceedings* 6:452-460, 1947.) This correspondence between skin and cerebral cortex probably also accounts for the beneficial effect of massage, another practice which originated in the Far East.

Divested of concepts of Yin and Yang and "vital essences," the idea of dermal representation in the cerebral cortex of internal organs may be far less fanciful than it appears at first glance.

While the Rasmussen-Penfield theory was not specifically intended to explain acupuncture, but may well be applied to it, other investigators have concentrated upon finding a physiological explanation for acupuncture analgesia.

As was to be expected, the arrival of modern Western scientific medicine in China reduced the importance of the disequilibrium of Yin and Yang as pathogenic factors and made it desirable to look for scientific reasons for the efficacy of acupuncture treatment. This is all the more the case since acupuncture has reached the Western World, and especially the United States. Most frequently quoted among the latter day investigators are R. Melzack of McGill University and Patrick Wall of the University College in London (*Science* 150, 1971, 1965) whose studies on the physiology of pain yielded the *"gate control theory."* (This so-called Melzack-Wall theory suggests that the pathway of pain to the brain is determined by a "gate control cell" in the substantia gelatinosa in the dorsal horn of the spinal cord.)

Although a certain element of scientific speculation remains in this proposition, a connection with acupuncture was developed on the basis of

the Melzack-Wall theory. According to reports of recent visitors to the People's Republic of China, Chinese investigators have been proceeding along this line of thought in considering the role of cortex, thalamus and hypothalamus, without, however, arriving at demonstrable conclusions. In the United States, two scientists in Michigan, Dr. Calvin H. Chen, a professor at Wayne State University and assistant medical superintendent at Northville State Hospital, and Dr. Pang L. Man of the same institution have postulated a concept to establish the thalamus as a second gate and have hence termed their hypothesis the "two-gate control theory."

It is important also to note that the latter theory states that acupuncture needles produce only a mild, fairly painless stimulation, causing the gates to be closed, so that painful sensations cannot pass through.

(Further speculations appeared in an article by H. C. Tien, entitled "Acupuncture Anesthesia: Neurogenic Interference Theory." *World Journal of Psychosynthesis* 1972, pp. 36-41.)

Such sophisticated deliberations were impossible to achieve by the traditional Chinese practitioners of acupuncture.

Without knowledge of the nature and the function of the central nervous system and the brain, which, as indicated before, was not considered among the major organs of the body, the early Chinese were incapable of fathoming a relationship between certain points on the skin and the cerebral cortex; therefore, they had to work with the concepts inherent in their philosophical theories of man's bodily function.

Still, in all probability none of the theories on the neurophysiological mechanism of acupuncture will be the last word in the explanation of the needling therapy. It remains to be seen whether a valid scientific basis for this mysterious operation will be established by investigators in the People's Republic of China or by Western researchers. So far it has eluded all students of acupuncture. In the meantime, however, a superabundance of clinical material at hand seems to demonstrate that acupuncture has proved effective in the alleviation of pain to untold multitudes of sufferers for thousands of years of therapeutic practice.

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Recapitulation of Minority Enrollment Programs of California Medical Schools

Based on replies to Spring 1972 Survey as applied to criteria adopted by the Councils of Golden State Medical Association and California Medical Association

NOTE: There have been changes at some of the schools since this survey was made but they were not available at the time of publication

GSMA-CMA CRITERIA	SCHOOL A	SCHOOL B	SCHOOL C
1. Each medical school in California should have or develop an active program to expand minority student enrollment in each entering class. (While a quota may or may not be desirable, the numbers of students from minority groups admitted to freshman classes of medical schools should be sufficient to project that within the reasonably near future the numbers of physicians among minority groups practicing in the community will reach some parity with the relative percentages of minorities in the population as a whole.)	Spring '72 enrollment—24.1 percent minority group members. Has minority group recruitment program with full-time recruiters and student aides. Has recruitment officer from minority group. Full-time faculty has 7.4 percent minority group members.	Spring '72 enrollment—22.3 percent minority group members. No minority group recruitment program per se. Uses Task Force Program which operates to provide opportunity to economically and educationally disadvantaged. Is attempting to increase representation among groups significantly under-represented in the health field. Has recruitment officer from minority group. Full-time faculty has 5.6 percent minority group members.	Spring '72 enrollment- percent minority group bers. Has minority grou cruitment program which sponsible for developing distributing brochures school, careers in med preparatory paths, etc. and personal contacts minority groups. Commu tion with actual and pot students re housing, fina aid, tutorials, etc. Has re ment officer from mi group. Full-time faculty 9.6 percent minority members.
2. The program should be designed to select students by some new criteria including elements that will allow minority students to compete with complete equality. In this it should be recognized that cultural, economic, social and ethnic differences often mask aptitudes in some students of high professional potential. and **3.** The program should be designed to help otherwise qualified persons meet necessary academic requirements.	Entrance requirement considerations: No weight given to ethnic background. Consideration given to economic status. There is program to assist minority students with admissions procedures. There is no quota for minority students. Quality of prior school is minor consideration. Has minority representation on Admissions Committee—7 faculty, 5 community representatives, 6 medical students. Has special committee which provides guidance/assistance to Admissions Committee in expediting acceptance of minority students.	Entrance requirement considerations: Weight given ethnic background varies; Black, Brown and Native Americans given priority by Task Force Committee. They look for demonstrable evidence or potential for helping disadvantaged peoples in the future. There is no quota for minority students. Quality of prior school is not considered. Has minority representation on Admissions Committee; (2) Has special committee which provides guidance/assistance to Admissions Committee—6 faculty, 18 students. 3 faculty and 3 students rate each applicant's chart and make recommendations to Admissions Committee after discussion with other Task Force members.	Entrance requirement co erations: Weight given background — minority applicants who would been screened out durin admissions routine are "s and handled by Minorit cruitment Subcommittee weighs non-cognitive fa early and intensively. Fa and administration have mitment to significantly crease opportunities for dents from disadvant backgrounds. Acceptance offered to one of ten mi candidates compared to of twenty-seven Cauca Emphasis on motivation, tudes, perseverance d adversity, personality, goals. Committee places reliance on peer judg There is no quota per aim for 15-20 minority dents per class. Quali prior school not consic Has minority representati Admissions Committee — 24-member faculty. Has cial committee which pro guidance/assistance to A sions Committee in ex ing acceptance of mi students.
4. Provision should be made for economic support where necessary.	Grants and loans available on basis of need. Loans from university funds allow for deferred interest payment if family income is below a prescribed level. The application fee is waived in hardship cases.	Grants and loans available. Some loans have low interest rate of 3 percent. The application fee is waived in hardship cases.	With two exceptions, and grants awarded on of need. University cann minister loans which dis inate on basis of race, or color. Minority studen encouraged to apply for loans as are reserved fo norities. The applicatio is waived in hardship c
5. The program should be designed to see to it that the accepted minority student does graduate because he did make the grade—not simply because of his minority group status, and not at some inferior level of competence, real or implied.	Provided is tutoring at the department level and counseling by one of the associate deans. There is no separate class for minority students accepted under special circumstances.	Tutoring is available; students are encouraged to see instructors if they feel need of additional help. Regularly arranged review sessions are available for any student desiring additional reviews. There is no separate class for minority students accepted under special circumstances.	Provided is a comprehe extensive series of tut of one faculty membe each one or two studer extend the amount of mation presented in co Additional tutorials focu learning skills and beh and on familiarization tests in diverse formats. is no separate class fo nority students accepted special circumstances.
6. Active programs of recruitment should be developed in California for students at the junior high school, high school and junior college level as well as at the four-year college and university campus.	Has counseling program at junior high school, high school, college and community levels.	Has counseling program at junior high school, high school levels. Has campus visitation program. Community contact on request.	Offers only informal co ing visits to junior schools. High schools re informal visits plus visi a recruiter. Colleges re direct, close and conti contact. Counseling is tained in the surrounding munity through sough relationships with variou nority groups and orga tions.

SCHOOL D	SCHOOL E	SCHOOL F	SCHOOL G	SCHOOL H
'72 enrollment—18.5 minority group mem- s minority group re- t program. Macy Re- Team contacts all ap- on the Med-Mar List ing their application. ority group recruit- icer. Full-time faculty cent minority group .	Spring '72 enrollment—15.1 percent minority group members. Has minority group recruitment program. A minority group recruitment office is staffed and welcomes questions and visits from interested persons. Has a recruitment officer from a minority group. Full-time faculty has 8.0 percent minority group members.	Spring '72 enrollment—14.3 percent minority group members. Has no recruitment program and no recruitment officer. Full-time faculty has less than 1.0 percent minority group members.	Spring 1972 enrollment—8.3 percent minority group members. Has minority group recruitment program administered by the Associate Dean of Admissions. Has a recruitment officer from a minority group. Information on percentage of minority group members on full-time faculty not available.	Spring '72 enrollment—6.6 percent minority group members. Has minority group recruitment program. Dean of Student Services arranges to interview promising minority candidates in their home area. Unknown as to whether there is recruitment officer from a minority group. Information on percentage of minority group members on full-time faculty not available.
requirement consid- Weight given to eth- kground—given con- n is his possible need worked while at- school, language dif- inferior secondary etc. There is no r minority students. of prior school is a ation. Has minority ation on Admissions e—2 doctors, 2 stu- as special committee ovides guidance/as- to Admissions Com- expediting accept- minority students—3 of Macy Recruiting	Entrance requirement considerations: Unknown as to whether weight is given to ethnic background. Academic record is important but special consideration for minority group candidates views motivation, personality, character, maturation, and present capacities in pre-med subjects as demonstrated in make-up courses. There is no quota for minority students. Quality of prior school not of importance per se, as applicant's total curricular experience is evaluated on an individual basis. Has minority representation on Admissions Committee—8 faculty, 4 students. Liasion Committee members (med school faculty, physicians from hospitals and the community, students who are active in minority recruiting) are available for counseling applicants who may need to supplement their educational backgrounds. Committee members can help place minority applicants in pre-med courses, when needed, on the campus et no cost to the student.	Entrance requirement considerations: Weight given to ethnic background considers origin of candidate and his ability to overcome educational and social deprivation. Looked for is capacity for self-identification, recognition of and sensitivity to minority problems, demonstrated efforts to help rectify problems when possible, and motivation. Quota for minority students is 12-14 positions offered through Minority Admissions Committee. Additional numbers may be admitted through Regular Admission Committee. Quality of prior school is a consideration since most minority students from Class A schools have better study habits and the ebility to cope with difficult curriculum. Minority representation on Admissions Committee is one. Has special Committee which provides guidance/assistance to Admissions Committee—8 faculty, 1 Assistant Dean, 5 students.	Entrance requirement considerations: Weight given to ethnic background; minority students accepted with lower GPA's and MCAT's than are others. Admission criteria for minority students allows them to compete for positions not open to others. Quota for minority students—positions allocated depending on size of incoming class. Quality of prior school not considered for applicants from a minority group. Minority group representation on the Admissions Committee is one. No special committee to provide guidance/assistance to Admissions Committee in expediting acceptance of minority students.	Entrance requirement considerations: Weight given to ethnic background; Admissions Committee interviews all minority group applicants (physically impossible to offer this service to every applicant). Letters of recommendation considered important evidence of student's motivation, leadership abilities, integrity and stability. Has no quota for minority students. Quality of prior school is given some weight but other criteria, such as GPA's of more import. No information on makeup of Admissions Committee available. No special committee to provide guidance/assistance to Admissions Committee in expediting acceptance of minority students.
nd loans are avail- e application fee is r minority applicants.	Scholarships, fellowships, loans and grants are available. The application fee is waived in hardship cases.	Loans and grants are awarded solely on the basis of demonstrated financial need. The application fee is waived in hardship cases.	Scholarships and loans are available. The application fee is waived in hardship cases.	Loans and grants are available. No information on possible waiver of the application fee.
is a one month tu- gram just before the he academic year to dents who may need ning of their science nd. During the aca- ar, tutoring by doc- students is aveilable having difficulty with culum. There is no class for minority accepted under spe- imstances.	A member of the faculty is designated as an "advocate" for students in academic jeopardy. Tutorials on a formal or informal basis from each department. These may be initiated by the student, the instructor or the advocate. A Prologue to Medicine is offered to incoming freshmen. There is no separate class for minority students accepted under special circumstances.	Special tutoring or counseling is provided on an informal basis by faculty, graduate students and current students. Details of program are defined in consultation between student and Associate Dean or between student and faculty advisor. There is no separate class for minority students accepted under special circumstances.	There are no arrangements for special tutoring or counseling. There is a separate class for minority students accepted under special circumstances—this class enables the student to take 50 percent of the typical student load in the first year, he then accelerates at the regular rate.	Student tutorial assistance and faculty counseling is offered. There is no separate class for minority students accepted under special circumstances.
nseling program at ool, college and com- evels.	Has counseling program at high school, college and community levels.	Has no recruitment or counseling program outside the school; however, under the Youth Opportunity Program, minority students have contact with medical students and faculty.	Has limited counseling program at the junior high school and high school levels. Offers extensive counseling et the college level. No community counseling.	Has no counseling program et junior high school or high school levels. Participates in a college recruitment effort and, when invited, visits colleges. Participates in community health fairs and other such activities.

Refer to: A membership program for residents and interns—A report to the CMA Council by the Commission on Communications, James C. MacLaggan, chairman. Calif Med 118:82-83, Feb 1973

California Medical Association

A Membership Program *for* Residents and Interns

*A Report to the Council by the Commission on Communications**

JAMES C. MacLAGGAN, MD, *Chairman*

THE COMMISSION ON COMMUNICATIONS was directed by the California Medical Association Council to develop a membership program for residents and interns. Through the commission's Subcommittee on Resident and Intern Membership, under the chairmanship of Ralph M. Milliken, MD, recommendations approved by the commission are submitted herewith. These recommendations have been concurred in by the Committee on Organizational Review and Planning, which considered the same matter under CMA House of Delegates Resolution 78-72.

Background

In the course of developing its proposal for resident and intern membership, the subcommittee obtained the cooperation of the directors of medical education for many housestaff training programs in the state in recommending representatives from their programs to meet with the subcommittee to discuss membership for residents and interns; met with these representatives at two meetings, one in Northern California and one in Southern California; surveyed component medical societies' present procedures concerning resident and intern membership; and met with executive directors of component societies in the counties with the largest numbers of residents and interns.

Deliberations

The subcommittee set as its goal a policy and program to attract residents and interns to unified membership in all three levels of organized medicine: county medical society, CMA, AMA. At the outset, it was recognized that many of the component societies accept residents and interns in various categories of membership, and some of the societies solicit them as members, but the success rate generally has been low.

It was necessary to determine what residents and interns wanted from organized medicine. Through the meetings with these housestaff members, and later with Dr. Eugene S. Ogrod, II, the AMA Residents and Interns Business Session's delegate, the subcommittee learned that many residents and interns are interested in joining organized medicine rather than the Physicians National Housestaff Association (formerly the National Coalition of House Staffs); that they

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want an effective voice, through full, active, voting membership with the right to committee assignments and to hold office; and that dues be assessed, but at a low level. It was further learned that residents and interns have virtually no knowledge about organized medicine or about the private practice of medicine, and that they have had little favorable exposure through their medical school faculties.

After lengthy deliberation, the commission believes that these are reasonable requests by residents and interns interested in joining organized medicine, and that they must be accommodated if a resident-intern membership campaign in California is to be successful.

To that end, the commission offers the following policy recommendations for consideration by Council:

1. *Recommendation:* That CMA Bylaws be amended to permit residents and interns to become active members of CMA with the right to vote and to hold office and membership on commissions, committees and advisory panels to the scientific sections of the Scientific Board, at reduced dues.

2. *Recommendation:* That it be CMA's policy to encourage resident and intern membership on CMA commissions, committees and advisory panels to the scientific sections of the Scientific Board.

3. *Recommendation:* That CMA Bylaws be amended to establish a component unit on residents and interns in which residents and interns who become members of component medical societies, CMA and AMA would hold concurrent membership. This component unit is to be established on a pilot project basis for a term of five years from the date it is approved by the CMA House of Delegates. At the annual meeting of the House one year before completion of this pilot project, it is to be reevaluated, with the House at that time deciding whether to end the project at the conclusion of the five-year period, extend the project or make the component unit permanent.

4. *Recommendation:* That, in those component medical societies without provision for active membership at reduced dues for residents and interns, residents and interns be permitted direct membership in CMA and its component unit on residents and interns until such time as active membership is available.

5. *Recommendation:* That members of the CMA component unit on residents and interns establish their own operating procedures, including those concerning administrative subdistricts, election of component unit officers and definition of "resident" and "intern" as regards eligibility for active membership in CMA and the component unit on residents and interns.

6. *Recommendation:* That the component unit on residents and interns seat a delegation of two delegates and two alternate delegates in the CMA House of Delegates to represent members of the component unit, and in addition seat one delegate and one alternate delegate for each 100 members or major fraction thereof beyond 200 members to represent residents and interns from counties where they are not eligible for active membership in component societies at reduced dues. Residents and interns may elect to vote and be counted for delegate representation either in their component medical societies or in the component unit on residents and interns, but not both.

7. *Recommendation:* That dues for residents and interns becoming active members of CMA and the component unit on residents and interns be set at $15 annually.

8. *Recommendation:* That CMA establish a committee on residents and interns, under the Commission on Member Services, to oversee CMA's resident and intern activities and to assist component medical societies, which will have the major role in recruiting residents and interns.

9. *Recommendation:* That CMA develop materials to assist it and the component medical societies in a resident and intern membership recruiting campaign. These materials may include a model letter of invitation to membership to be sent to each resident and intern in California; a model letter to be sent to directors of medical education and/or housestaff presidents requesting the opportunity for a component medical society speaker to address housestaff meetings; a model speech for use by component medical society representatives at housestaff meetings; and a package of materials to be distributed at housestaff meetings, the materials to include a pamphlet on the activities of organized medicine and its benefits to members and the public, and a socioeconomic orientation handbook.

10. *Recommendation:* That CMA's component medical societies be urged to establish and actively implement appropriate policies parallel to those recommended above.

11. *Recommendation:* That the above recommendations be transmitted to the CMA House of Delegates for consideration at its next annual meeting.

PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Director, State Department of Public Health

Hyaline Membrane Disease

BECAUSE OF THE CATASTROPHIC COSTS of care to young parents of infants with hyaline membrane disease (HMD) and the belief that specialized centers for the care of this condition would lower mortality, attempts have been made through the years to make HMD eligible for care under the State's Crippled Children Services program (CCS). However, costs of care for the estimated eligible caseload were thought to be too great for CCS to absorb without special appropriations, and these early attempts were unsuccessful.

In 1967, an Assembly Concurrent Resolution 108 (Vasconcellos) directed the State Health Department's Bureau of Crippled Children Services to study the disease, its treatment and its costs. The study reported that 4,000 infants a year in California were born with HMD, that the overall mortality was 70 percent for those who received only routine newborn care, and about 50 percent for infants who received care in infants intensive care units (IICU's).

The following year, AB 1413 (Vasconcellos) directed the Department to analyze the treatment and outcome of HMD before and after the development of intensive care and to compare the costs. The Department's Bureau of Maternal and Child Health carried out a three-year investigation, including a retrospective study of 352 infants with HMD who received routine nursing care in 1965 and a prospective study of 514 infants with HMD born in 1969-70 who were either born in hospitals with IICU's or transferred to them during their first few hours.

This study showed a 10 percent reduction in mortality for those who received care in IICU's, a saving of 400 lives a year. The average cost for infants treated in IICU's in 1969-70 was $2,588 per infant, or $3,500 for each infant who survived. It was estimated that it would cost California $5 million a year to care for infants with HMD who were eligible for Crippled Children Services. The report recommended that IICU's be established throughout the state, that the concept of identification of high risk mothers and infants be developed so that infants at risk could be delivered in hospitals with IICU's and that methods of funding such care be developed.

As a result of this study, AB 3003 (1971 Vasconcellos) was introduced, making HMD an eligible condition under the Crippled Children Services program. The bill was passed and signed by the Governor, taking effect in March 1972, and $800,000 was appropriated for the remainder of that fiscal year.

The Bureau of Crippled Children Services has since developed standards for IICU's, appropriate not only for HMD infants but for the care of any infant ill enough to require such specialized skills. The program is primarily concerned with HMD infants who require the special skills available only in an IICU.

The following requirements for IICU's have been developed:

1. A unit shall be in a hospital approved for CCS for long-term care.
2. The unit shall be directed by a CCS panel pediatrician specializing in neonatology, whose primary responsibility is the unit.
3. All nursing personnel must have specialized training in intensive care of the newborn, and there must be adequate nursing personnel to offer one-to-one coverage around the clock if necessary.

4. A physician whose primary responsibility is the unit shall be in the house and available to the unit on a 24-hour basis.

5. A pediatric surgeon shall be available to the unit.

6. A medical social worker, having a master's degree in social work, and a public health nurse shall be participating members of the nursery unit.

7. The unit neonatologist takes the responsibility of transferring and choosing the method of transfer to the unit, and close liaison is maintained between the unit staff and the nursery staff of the referring hospitals.

The Department and the Perinatal Mortality Subcommittee of the California Medical Association have been developing standards for transport of newborns to intensive care units and for such equipment as incubators. The ideal transport team should have a minimum of two persons, such as physicians, nurses and interns, available 24 hours a day, seven days a week. Transport to the IICU may be by special van, such as those of the mobile units which operate out of San Francisco's Children's Hospital, Sacramento Medical Center, and Loma Linda University's Medical School; but ambulances, helicopters, planes, and trains may also transport such infants.

Currently 18 IICU's have been approved by the Bureau of Crippled Children Services. After six months' experience in the coverage of this condition, the bureau decided to expand the program to reach those infants with HMD cared for in communities which are unable to meet standards for an IICU. Approval is based on a commitment by the community to centralize high risk maternal and neonatal care in one hospital and is contingent upon a close working relationship with the neonatologist in an approved IICU.

make reservations now and plan to attend . . .

CMA PRESIDENTS' DINNER

SUNDAY EVENING, MARCH 11 • DISNEYLAND HOTEL, ANAHEIM

Dinner will be at 7:30 p.m., immediately following the traditional Presidents' Reception at the CMA Annual Session, and the leaders of the CMA and the Woman's Auxiliary to the CMA will be honored. The dinner will feature live music, entertainment, and awards and presentations formerly made during the House of Delegates sessions.

Tables seat 10 persons

Tickets are $10.50 each

For reservations, send check made out to WA-CMA to:

WOMAN'S AUXILIARY TO CMA
10161 Broadview Place
Santa Ana 92705

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

DEMPSEY, THOMAS F., San Bernardino. Died December 1, 1972 in San Bernardino, aged 61. Graduate of University of Southern California School of Medicine, Los Angeles, 1938. Licensed in California in 1939. Doctor Dempsey was a member of the San Bernardino County Medical Society.

DUGGAN, RICHARD J., San Francisco. Died December 25, 1972 in San Francisco, aged 66. Graduate of the Creighton University School of Medicine, Omaha, 1931. Licensed in California in 1931. Doctor Duggan was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

DUNLAVY, KENNETH J., Healdsburg. Died November 22, 1972 in Healdsburg of heart disease, aged 67. Graduate of University of Colorado School of Medicine, Denver, 1931. Licensed in California in 1933. Doctor Dunlavy was a retired member of the Sonoma County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

ELKINS, HARRY K., Los Altos. Died November 28, 1972 in Mountain View, aged 60. Graduate of University of Wisconsin Medical School, Madison, 1939. Licensed in California in 1941. Doctor Elkins was an associate member of the Santa Clara County Medical Society.

HAMREN, JOHN MORGAN, Vallejo. Died between Byron and Stockton when his car crashed and burned December 14, 1972, aged 48. Graduate of the University of California at Los Angeles School of Medicine, 1958. Licensed in California in 1959. Dr. Hamren was a member of the Solano County Medical Society.

HEWKO, JOSEPH W., Montebello. Died November 21, 1972 in Montebello, aged 51. Graduate of McGill University Faculty of Medicine, Montreal, 1948. Licensed in California in 1949. Doctor Hewko was a member of the Los Angeles County Medical Association.

KARR, MARTIN, San Mateo. Died January 3, 1973, aged 67. Graduate of the University of Louisville School of Medicine, 1932. Licensed in California in 1933. Doctor Karr was a member of the San Mateo County Medical Society.

LEIMBACH, JOHN HERBERT, JR., Piedmont. Died May 19, 1972 in Berkeley of carcinoma of the liver, aged 66. Graduate of McGill University Faculty of Medicine, Montreal, 1937. Licensed in California in 1937. Doctor Leimbach was an associate member of the San Francisco Medical Society.

MANNING, JOHN BROWN, JR., Santa Barbara. Died December 26, 1972 in Santa Barbara, aged 57. Graduate of Cornell University Medical College, New York, 1943. Licensed in California in 1950. Doctor Manning was a member of the Santa Barbara County Medical Society.

PERSELL, LOUIS S., Pasadena. Died December 1, 1972 of heart disease, aged 68. Graduate of St. Louis University School of Medicine, 1935. Licensed in California in 1944. Doctor Persell was a member of the Los Angeles County Medical Association.

SWAN, JAMES EDWARD, Los Angeles. Died November 27, 1972, aged 52. Graduate of Howard University College of Medicine, Washington, D.C., 1948. Licensed in California in 1953. Doctor Swan was a member of the Los Angeles County Medical Association.

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Travelers' Diarrhea

ELIZABETH BARRETT-CONNOR, MD, *San Diego*

On the average, one-fourth of North Americans visiting developing countries experience a self-limited diarrheal illness that interferes with holiday or business activities. Recent work suggests that these episodes are caused by a small inoculum of enteropathogenic Escherichia coli which are common in the country visited and rare in the country of origin. Neither antimicrobial treatment nor anti-diarrheal agents have proven benefit once the illness has begun. Despite its frequent use, iodochlorhydroxyquin has not been shown in double blind studies to be effective as a preventive agent, and may be dangerous. The status of furazolidone for prevention of tourist diarrhea is questionable. Both neomycin sulfate and phythalylsulfathiazole have demonstrated efficacy as chemoprophylactics in Mexico. However, their use should be restricted to limited types of travel and travelers.

General admonitions concerning avoidance of certain ingestibles are recommended; despite questionable value in preventing travelers' diarrhea such precautions may prevent more serious gastrointestinal illness.

MORE THAN four and half million American citizens left the United States in 1970 for foreign countries, excluding trips to Europe and border crossings, according to the U.S. Travel Service. Last year nearly 25,000,000 border crossings were made into Tiajuana alone. Travel to countries other than Canada and Northern Europe is associated with a number of medical hazards, the most common if least serious of which is travelers' diarrhea. Athough traditionally the traveler experiencing this syndrome was better informed as to its nature than the average physician, a number of recent investigations have at last shed some scientific light on the cause, characteristics and possible prevention of this illness.

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Submitted October 27, 1972.

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Epidemiology

The frequency of travelers' diarrhea varies with the age of the traveler, the country visited, and the country of origin of the traveler. Both sexes are equally susceptible, although the risk appears to

decrease with age.[1] The lowest and the highest reported incidences were derived from retrospective studies; 7.5 percent of air travelers returning from Hawaii to the United States and 71 percent of American students returning from the Mediterranean by ship reported tourist diarrhea.[2,3] In prospective and retrospective studies of North Americans visiting Mexico City, one-fourth to one-third had tourist diarrhea.[1,4,5] Travelers' diarrhea is most common in persons from northern industrialized nations visting warmer and less sanitated countries. Thus, United Nations observers from Europe and North America experienced significantly more diarrhea when dispersed throughout Lebanon than did those observers originating from Asia and South America.[6] Similarly, only 8 percent of 163 travelers from tropical countries visiting a medical congress in Teheran had diarrhea, against 41 percent of 230 from countries with more temperate climates. These observations suggest that immunity plays a role in travelers' diarrhea and supports the concept that the disease is caused by an infectious agent. Two-thirds of affected persons become ill within the first two weeks of travel, but diarrhea is rare in the first three days;[2] this apparent incubation period also makes infection a probable cause.

Signs and Symptoms

The symptoms are remarkably similar whereever travelers' diarrhea is acquired. Non-bloody diarrhea, with or without nausea, vomiting, abdominal pain and malaise are typical. Although not generally considered to be a febrile illness, subjective fever complicates three-fourths of cases occurring in Mexico, and chills occur in half.[2] Severity varies from a few diarrheal stools which do not interfere with activity to an illness of longer than three days. However, the latter occurs in less than 15 percent of cases.[2] Nevertheless, one-third of affected travelers are sufficiently prostrated or "toilet-bound" to be confined to quarters for one to three days.[2] Patients generally appear tired and weak, but physical examination reveals little except low-grade fever and occasional tenderness over the transverse colon.

Cause

Patients in whom symptoms, physical findings or duration of illness do not fit this pattern are arbitrarily excluded from a diagnosis of travelers' diarrhea, and may have salmonellosis, shigellosis, giardiasis or amebiasis. These pathogens, however, are not responsible for more than 5 to 15 percent of enteric illness in travelers, the vast majority of whom have no shigella, salmonella, parasites or viruses recovered from stool.[3,8-11] The exclusion of viral infection as a cause is always suspect, in that available culture techniques may not permit recovery of all agents. Nevertheless, the apparent preventive effect of antimicrobials (vide infra) supports suspicion of bacterial rather than viral infection. Current work suggests that this disease is caused by enteropathogenic Escherischia coli; earlier failures to demonstrate this association were caused by limiting the search to recognized infantile pathogenic serotypes.[8] Recently a new serotype of E. coli with antigenic structure 0148: H28 was demonstrated in about half of 35 acute cases of diarrhea occurring in British soldiers during their first 14 days after arrival in Aden.[11] This serotype was never isolated from healthy subjects. Pathogenicity of this serotype for adults was demonstrated when a technician working in England, where the serotype is not found, acquired a laboratory infection and had severe diarrhea; E. coli 0148:H28 was recovered in pure culture from the stool. This exciting work suggests that in "any investigation (of travelers' diarrhea) E. coli strains must be fully serotyped and workers must be prepared to identify new serotypes and determine their relation to diarrhea."[11] Although it seems likely that a variety of serotypes will ultimately be found to be responsible for travelers' diarrhea in different parts of the world, and indeed in the same place at different times, the lower attack rates in travelers from other tropical or semi-tropical climates could be interpreted as evidence for immunity to like organisms.

Treatment

Therapy for this self-limited illness is without demonstrated benefit. Since few patients are ill for more than three days, success can be attributed to almost any medication taken. Antimicrobials may cause untoward reactions or mask more serious disease and cannot be recommended for tourist diarrhea of less than three days' duration. Persons ill for longer periods deserve microscopic and cultural examination of stool rather than empirical use of antibiotics. The value of non-specific anti-diarrheal agents designed to reduce the frequency of bowel movements is similarly unproven, although anecdotal

experience suggests that they may relieve the debilitating effects of fluid and electrolyte loss. There is, however, a theoretical reason why such agents are undesirable in that unchecked diarrhea may serve to cleanse the bowel of the infecting agent. It has been shown that enterotoxin-producing E. coli, like 0148:H28, and the enterotoxin itself are not firmly bound to the bowel mucosa and can be washed out.[12,13]

Prevention

Many travelers—up to 40 percent in one retrospective study of air travelers to Mexico—self-medicate themselves with prescription or proprietary agents in hopes of either preventing or minimizing the severity of tourist diarrhea.[1] Several controlled studies have been conducted in an effort to evaluate the prophylactic value of specific agents against travelers' diarrhea (Table 1).

Iodochlorhydroxyquin (Entero-vioform®, Vioform,® clioquinol) has probably been the most widely used.[7] The use of this agent may have begun with the mistaken belief that tourist diarrhea was amebic in origin and belief in it perpetuated by the self-limited nature of the illness. The fact is that double blind randomized study of North American students in Mexico City showed the incidence of diarrhea to be significantly greater in travelers taking iodochlorhydroxyquin than in those taking placebo.[4] In contrast, Richards reported a significant reduction of diarrhea in athletes traveling mainly to European countries, when iodochlorhydroxyquin was taken prophylactically.[14,15] These studies are not entirely satisfactory in that they were neither double blind nor randomized. In addition the results do not distinguish very mild gastrointestinal upset from more severe diarrhea, and the reduction could be attributed in part to the lessening of bowel gas through use of this drug.[16] In addition, the safety of iodochlorhydroxyquin is questionable. Scandinavian tourists visiting Mediterranean countries who regularly used oxyquinolines prophylactically acquired salmonellosis significantly more often than tourists not taking this drug.[17] Further, Japanese studies strongly suggest that a severe and not necessarily reversable neurologic syndrome, subacute myelo-optic neuropathy (SMON), is related directly or indirectly to the use of clioquinol: 85 percent of persons in whom SMON developed had taken clioquinol, the risk was dose related, and the syndrome nearly disappeared following discontinuance of this drug.[18] Unfortunately, the traditional use of this agent and its non-prescription status in many countries, suggest that iodochlorhydroxyquin will continue to be used for tourist diarrhea despite its doubtful efficacy and possible dangers.

A double blind study of Royal Air Force men visiting countries east of the Mediterranean showed furazolidone to be effective as a chemoprophylactic agent against tourist diarrhea.[19] In Mexico, diarrhea developed in two of seven teachers from New York who were taking no drug while none of ten teachers taking 400 mg of furazolidone daily for two weeks had the disease, although seven complained of continual nausea.[2] In an uncontrolled study, eight of eleven travelers to Mexico developed diarrhea despite furazolidone, 200 mg daily.[2] The status of this drug for the pro-

TABLE 1.—*Controlled Studies of Chemoprophylaxis for Travelers' Diarrhea*

Drug	*Diarrhea With Drug*	*Diarrhea With Placebo*	*Study Population*
Iodochlorhydroxyquin 250 mg bid, tid or qid (3 studies combined)...	16 of 499 (3.21%)	42 of 279 (15.5%)	Mainly male athletes, world travel[14]
Iodochlorhydroxyquin 375 mg bid.	81 of 210 (38.6 %) *34 of 210 (16.2 %)**	68 of 202 (33.6%) *22 of 202 (10.9%)**	U.S. students in Mexico[4]
Neomycin sulfate 375 or 500 mg bid (2 studies combined).....	62 of 335 (18.5 %) *20 of 335 (5.97%)*	108 of 370 (29.2%) *51 of 370 (13.8%)*	U.S. students in Mexico[4,5]
Furazolidone 100 or 200 mg qd..	*28 of 407 (6.88%)*	*57 of 201 (28.4%)*	Royal Air Force males east of Mediterranean[19]
Phthalylsulfathiazole 1 gm bid...	20 of 168 (11.9 %) *11 of 168 (6.55%)*	40 of 168 (23.8%) *29 of 168 (17.3%)*	U.S. students in Mexico[5]

NOTE: Data in roman letters refers to all degrees of diarrheal illness. Data in italics refers to diarrhea of severity to interfere with daily activity or to require medical treatment.

*All differences are statistically significant (t test) except this value.

phylaxis of tourist diarrhea, therefore, remains in doubt.

Both neomycin sulfate and phthalsulfathiazole have been shown in good drug trials to reduce the risk of tourist diarrhea significantly in Mexico.[5] It remains to be seen whether these drugs would be beneficial in other parts of the world. The only other study (of British Overseas Airways Corporation personnel and their families going abroad who were said to have found no protection in a neomycin-sulfonamide combination) is unsatisfactory in that specific data are not presented.[20]

Physicians recommending chemoprophylaxis should consider the risk of drug, the risk of turista, and the duration and purpose of the visit. Persons planning a short visit to Latin America, when the purpose of the trip would be seriously impeded by the development of tourist diarrhea, and when there is no medical contraindication to neomycin or phthasulfathiazole, can be offered chemoprophylaxis. Persons traveling for more than three weeks are rarely if ever candidates for prolonged chemoprophylaxis.

No drug is wholly effective in preventing travelers' diarrhea. Therefore, whether or not drug prophylaxis is used, the traveler should be advised about general precautions. These include the avoidance of local water supplies, including ice. Safe bottled liquids are those that are sealed (more than one traveler has returned to the hotel to find the maid refilling the "bottled water" from the tap). It is also recommended that travelers avoid fresh fruit and vegetables unless they are cooked or can be peeled. Many physicians advise travelers to avoid spicy or unusual native dishes and excessive fatigue and alcohol, although few heed these admonitions. All these recommendations make sense, but there is little information to support their efficacy. A study by the Center for Disease Control of persons attending a medical congress in Mexico City showed no difference in the attack rates of diarrhea in those who ate and drank without precautions than in those who drank only bottled liquids and avoided salads and the like.[21] This information is compatible with the hypothesis that ubiquitous E. coli of serotypes foreign to the traveler are responsible for the disease, and that only a small inoculum is required to produce illness. Nevertheless physicians should continue to make the same general recommendations to travelers, in the hope that such measures will at least reduce the risk of acquiring more serious gastrointestinal infections.

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National Surgical Breast Project

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For public and professional acceptance, clinical studies in breast cancer must be scientifically necessary and ethically justifiable. To resolve controversy based upon retrospective data, they must be prospective and randomized. These guidelines have been used by the National Surgical Adjuvant Breast Project in its investigations carried out during the past 15 years in numerous cooperating institutions. Neither thio-tepa adjuvant to radical mastectomy, nor prophylactic oophorectomy, nor postoperative radiation therapy were found to prolong life. Therefore, prophylactic oophorectomy is contraindicated and adjuvant chemotherapy cannot be justified except perhaps under special circumstances and as part of carefully controlled clinical trials. Postoperative radiation therapy, even in the presence of positive axillary lymph nodes, cannot be recommended except to minimize the rate of local skin recurrences.

The present study addresses itself to the timely controversy surrounding proper management of axillary lymph nodes in primary breast cancer. Does removing them alter the outcome of therapy? Total (simple) mastectomy is being compared with radical mastectomy. Women with clinically negative nodes on physical examination are treated either by total (simple) mastectomy alone or by total mastectomy plus radiation, or by radical mastectomy. When the nodes are clinically positive, either radical mastectomy or total mastectomy followed by radiation is being used.

The protocol, now underway more than a year, has been well accepted by patients and by many well informed physicians and surgeons. In years ahead it will provide objective evidence as to whether or not removal of the axillary lymph nodes alters the therapeutic efficacy of mastectomy in the treatment of primary breast cancer.

The National Surgical Adjuvant Breast Program is a cooperative study involving investigators scattered throughout the country. Most of the participating institutions are university hospitals, but some private institutions also participate. This project has been sponsored by the National Institutes of Health, and participation in the studies is therefore open to any institution which qualifies.

Before tracing the history of this program, let me review what I consider requirements for any clinical study dealing with breast cancer: It must be scientifically necessary and ethically justifiable. The therapeutic methods to be compared against each other must be generally acceptable to a responsible segment of the professional community. If there is agreement that the study is scientifically necessary and ethically justifiable, then it must be prospective, randomized and carefully controlled lest the data which derives from it be subject to skepticism and criticism. The fact that these last three principles have not been well recognized over the years in large part explains the current controversies related to the treatment of breast cancer and the fact that the thousands of publications on the subject have not been able to resolve these controversies in a generally acceptable manner.

In 1957, the National Surgical Adjuvant Breast Project was begun for the purpose of testing the concept of administering chemotherapeutic agents systemically in conjunction with operation in an effort to decrease the recurrence rate and to enhance the survival rate among patients with breast cancer. Appealing and logical as this concept is, it was felt to be scientifically necessary and ethically justifiable to subject it to test by taking patients with apparently curable breast cancer, all of whom were treated with standard radical mastectomy. In addition, they were randomly allocated either into a group treated with adjuvant thio-tepa or into a control group treated with adjuvant placebo. Four years later, three additional cooperative studies were begun. The first tested the efficacy of thio-tepa as compared with 5-fluorouracil, and the second tested the hypothesis that prophylactic oophorectomy is beneficial to women with breast cancer. The third study, begun in 1961, evaluated the effects of postoperative radiotherapy as an adjunct to radical mastectomy. Then there was a ten-year gap before the current study in which radical mastectomy is being compared with simple mastectomy. Some of the findings and some of the details of each of these studies will be reported here, and for those who wish to pursue the subject further, I have prepared a selected bibliography of publications resulting from these studies.[1-5]

First the study in which thio-tepa was compared to a placebo adjuvant to radical mastectomy:[1] A five-year follow-up study of 826 patients was completed. The data were analyzed in a variety of ways, including the subdivision of patients into premenopausal and postmenopausal. Each of the small differences was subjected to statistical analysis and no significant differences were found between any of these groups except in the very special circumstances of premenopausal women in whom four or more axillary lymph nodes contained cancer. In that group of women, the recurrence rate between the 18th and 36th postoperative months was approximately 40 percent less than in the placebo group, and this difference was statistically significant. However, by 48 months the placebo group and the thio-tepa treated group were no longer significantly different. The second protocol in which 5-fluorouracil was compared with thio-tepa as an adjuvant to radical mastectomy had to be abandoned prematurely because the incidence of local and systemic complications in patients who received adjuvant 5-fluorouracil was unacceptable.

If I were to make a summary statement concerning adjuvant chemotherapy as tested in these studies, I would have to say that they provide no justification for the use of either 5-fluorouracil or thio-tepa in post-menopausal women with or without positive axillary nodes. The use of thio-tepa in the premenopausal patients with four or more positive axillary lymph nodes can be justified if one is willing to accept some discomfort, inconvenience and risk for the purpose of a short-term gain without the promise of lasting benefit. At present I support Dr. Bernard Fisher's statement that "the use of adjuvant chemotheray by surgeons in any other setting than a clinical trial must be looked upon as therapeutic adventurism and should be condemned."[4]

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From the Department of Surgery, Harbor General Hospital, Torrance, and the University of California, Los Angeles, School of Medicine.

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Let us look now at the findings from 357 women in whom prophylactic oophorectomy was evaluated.[3] Although superficial analysis might have suggested that prophylactic oophorectomy in women with negative nodes gave a higher recurrence rate than treatment with a placebo, statistical analysis demonstrated no significant difference. In women with positive nodes, the patients with prophylactic oophorectomy at one and two years after operation appeared perhaps to have a slightly lower recurrence rate than the patients treated with placebo, but again these differences were more apparent than real. If one looked at these data from the viewpoint of survival, no significant difference was found between patients treated with prophylactic oophorectomy and those treated with adjuvant placebo. Indeed, superficial analysis suggested that the placebo-treated patients did better than those with oophorectomy. From these findings it was concluded that there is no justification for the use of prophylactic oophorectomy in the treatment of apparently curable breast cancer.

Now let us turn to the study of the effect of postoperative radiation therapy in 1,103 patients.[2] An analysis of treatment failures showed no significant difference in disease recurrence or survival rates between patients receiving radiation therapy and those serving as controls at three, four or five years following operation. Regional and local recurrences were significantly less in patients receiving postoperative irradiation than in controls. As to the survival of women with positive nodes following radical mastectomy treated either with or without radiation therapy, no significant difference was found between the treated and the placebo group. Since local control does not determine the fate of patients with breast cancer, this study demonstrated no advantage of postoperative radiation as an adjuvant to operation in apparently curable breast cancer.

Before going on to current protocols, I would like to summarize the data from those which have been completed and published. There really were only two findings of benefit from the adjunctive methods of therapy tested. Thio-tepa in premenopausal women was found to be helpful in delaying recurrence rates when there were more than four positive nodes present but this benefit was temporary and transient. Adjuvant radiation therapy, even in women with positive nodes, was beneficial only in the sense that the incidence of local recurrence was decreased in those patients who were treated with x-ray as compared with controls. With regard to survival results, thio-tepa adjuvant to radical mastectomy was of no benefit as compared with placebo. Nor was 5-fluorouracil helpful as an adjuvant, and its use was prematurely discontinued because this part of the study was no longer ethically justifiable. Prophylactic oophorectomy was found to be of no benefit. Similarly, postoperative radiation therapy, even in women with positive axillary lymph nodes, did not improve results.

The current protocol is addressed to the question of whether or not radical mastectomy is necessary and justifiable. Clearly, even unsightly results may be easily justified if they promise a better chance of cure than less extensive operations. But the lay population in general and the medical profession as well are sufficiently confused about the proper operation for apparently curable breast cancer to make a study along these lines both scientifically necessary and ethically justifiable.

Let us return for a moment to 1955 when there was essentially no controversy, in that fully trained surgeons almost universally accepted the Halsted radical mastectomy. Haagenson's results with radical in patients with clinical Stage A where the disease was limited to the breast were a 70.2 percent ten-year survival rate.[6] When the cancer had spread beyond the breast, the cure rates with radical mastectomy were considerably lower although still quite respectable. In general, surgeons who went through training in the late 1950's and early 1960's accepted radical mastectomy as the treatment of choice.

In 1955, McWhirter published therapeutic results of simple mastectomy supplemented with radiotherapy with the rationale that radiation could attack the involved lymph nodes in a more radical fashion than any operation could hope to achieve.[7] It is interesting that although he considered his proposal a radical one, the remainder of the medical community over the ensuing years came to view it as one of the first signs of a more conservative approach to the treatment of breast cancer. In any event, McWhirter achieved survival rates almost as good as those associated with radical mastectomy. In practice, I daresay that even the most radical surgeon has at times resorted to simple mastectomy supplemented with radiation in patients who were believed not suitable candidates for radical mastectomy. McWhirter's data

cannot be analyzed in detail here; they are presented because they were among the earliest and most serious challenges to the concept of radical mastectomy.

In 1959, Smith and Meyer[8] reviewed data from Rockford, Illinois, during the war years, when the number of fully trained surgeons in that middle western community was sharply limited, and compared the results of radical mastectomy done by fully trained surgeons with the results of simple mastectomies, most of which were done by occasional surgeons. They found that patients with simple mastectomy had done better than those with the radical operation. However, their study was not convincing because it was totally retrospective and because radiation was given in a variety of ways to unstated numbers in both groups. More, it can be argued that during those war years the patients with the most advanced and challenging tumors were undoubtedly referred to the fully trained surgeons who practiced radical mastectomy, thereby introducing an unfair bias in the patient selection for the two groups. Nevertheless, the challenge to established therapy had been raised by McWhirter and carried further by Smith and Meyer.

Nine years later, Crile presented a paper before the American Surgical Association in which 62 patients with radical mastectomy were compared with 69 patients who had simple mastectomy and the results in the simple were better than in the radical mastectomy group.[9] However, the selection criteria were not clear and the comparisons were inconclusive in that Crile compared his own patients with those of others; and the discussion which followed the presentation of his paper reflected the fact that he certainly had not settled any issues to the satisfaction of some of the leaders of American surgery.

Undaunted and convinced that he was correct, Crile continued his work. Indeed, he extended it to the point where one of his recent publications reports on 40 patients with Stage I breast cancer who were treated by local excision[10] with a 67 percent five-year survival rate. If one reads his paper critically, the results are provocative and must not be ignored but they are not convincing. For example, some patients received adjunctive radiation therapy and others did not and his studies have certainly not met all the requirements for clinical breast cancer studies which I set forth at the beginning. The patients were not randomly selected, and there were not appropriate controls.

In Britain there has been a prospective randomized study in which simple and radical mastectomy were compared and the data suggested that simple mastectomy was better than radical mastectomy.[11] However, if one analyzes these data carefully, one finds that the study is not sound enough scientifically to resolve the controversy. For example, the so-called simple mastectomy included axillary lymph nodes, and radiation therapy was given to all the patients. Although Brinkley and Haybittle concluded that their evidence favored simple mastectomy, they have redesigned their study in order to resolve the same controversy to which the National Surgical Adjuvant Breast Project is currently addressing itself.

The current protocol does not seek to answer all questions relative to breast cancer. It simply wishes to provide scientifically sound and ethically justifiable data with which to guide surgeons who are charged with the responsibility of selecting the proper operation for women with breast cancer. As we developed this protocol, it was interesting to note three broad groups of physicians. There were those who participated in protocol design originally and then withdrew, stating they could not justify doing anything less than a radical mastectomy for breast carcinoma, while at the other end of the spectrum there were those who withdrew saying essentially that they could not justify subjecting patients to a radical mastectomy. The third group, which includes me, felt that a study comparing radical mastectomy with other forms of apparently acceptable therapy was scientifically extremely necessary and ethically entirely justifiable.

The following prospective randomized controlled study has therefore been under way for almost a year: On the basis of physical examination and customary workup, each patient is classified as having clinically negative nodes or clinically positive nodes. Those in whom the nodes are negative, are treated either by total (simple) mastectomy alone, or by total (simple) mastectomy plus radiation, or by radical mastectomy. Those who on physical examination appear to have positive nodes are randomly allocated to receive either total mastectomy followed by radiation, or standard radical mastectomy. Control mechanisms have been set up to make this randomization procedure entirely honest. If there are medical or other reasons why a given patient should not be put into

the study, the reason for the elimination is stated and the elimination is made before randomization. Frequently voiced misgivings as to whether patients and referring physicians would accept such a program have proved groundless. The program has had the most careful and repetitive scrutiny at the National Institutes of Health, and I think we can look forward to some valuable results in years ahead.

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Refer to: Manchester GH: Tattoo removal—A new simple technique. Calif Med 118:10-12, Mar 1973

Table salt applied by salabrasion, tattooing or dermabrasion was used in the treatment of unwanted tattoos in 25 cases. With removal of the eschar at the treated site, the unwanted pigmentation was reduced by half, and there was further dimming to virtual disappearance during further healing.

Tattoo Removal

A New Simple Technique

GARY H. MANCHESTER, MD
San Diego

THE PROBLEM OF TATTOO REMOVAL has been with man a long time. History records the Egyptians in 4000 B.C. to be the first to use tattoos for identification of their social classes.[1] This practice was revived by Hitler to recognize the enemies of the Third Reich, while inmates of our penal institutions use the self-inflicted ink tattoo for initiation of a new prisoner.

Tattooing as a decorative and artistic form first found expression in Europe at the end of the 19th century. Lady Randolph Churchill is said to have had a snake placed around her arm. This art form found great acceptance with the American service man as an expression of his manhood during the past century.

After World War II, the incidence of tattoos began to decline. Social pressures were brought to bear in the large cities, and health departments began closing down the "art parlors." The medical literature was busy reporting the transmission of syphilis, tuberculosis, and infectious hepatitis through the use of the tattoo needle.[1-3] In 1948 Bromberg published his psychiatric study of the tattooed personality.[4] Dr. Bromberg concluded that emotional instability was the underlying cause for this self-embellishment. He felt that the tattoo was either a form of exhibitionism or the means for a weak neurotic to associate himself with a strong group of people—soldiers. With this report and the public awareness of a problem, employers began refusing positions of responsibility on the basis of a previous indiscretion. In 1969 the United Kingdom passed a law restricting the use of tattooing in minors.[5]

Recently requests for tattoo removal have increased greatly in the United States due to the use of these markings in the initiation rites of the various Hippie-Yippie cults. With the increased demand, I found myself without a means of removing tattoos quickly and inexpensively. Approximately two years ago, I began experimenting, with the patients' permission, on new methods for tattoo removal.

The basic problem is that the accepted methods of treatment—serial excision or excision and grafting—either cause a spread or an unsightly scar, or trade one blemish for two defects. Since 54 A.D., physicians have tried to remove tattoos without leaving a scar. Aetius (543 A.D.) was the first to describe the use of salt and chemicals for the purpose.[5] Klövekorn (1935) described the abrasion of skin with table salt in order to remove tattoo pigment;[6] and Crittenden recently confirmed these results and named the process *salabrasion*.[7] Salabrasion, the removal of tattoos by superficial abrasion of the skin with table salt, is merely one means of delivering sodium chloride to the underlying dermis. I have found that salabrasion, dermabrasion, and tattooing with table salt or a salt solution give equally good results with minimal scarring.

Technique

The area to be treated is first shaved and prepared with Phisohex®. A local anesthetic is then infiltrated into the skin when a dermabrador or

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Reprint requests to: G. H. Manchester, MD, 7910 A. Frost Street, Suite 205, San Diego, Ca. 92123.

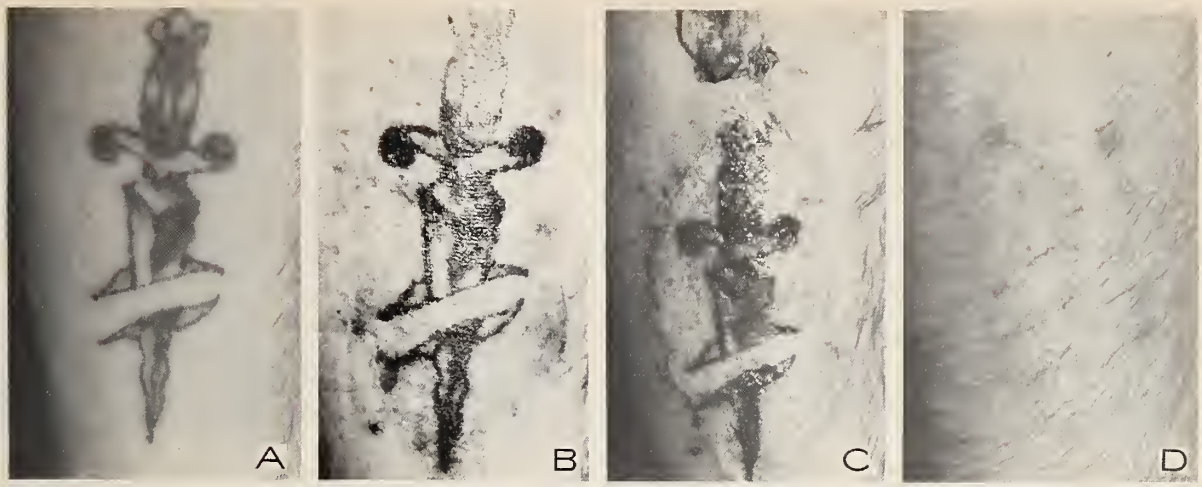


Figure 1.—A. a six-year-old multicolor tattoo before treatment. **B.** 72 hours after abrasion with table salt, the treated area has the characterstics of tanned leather. **C.** on the eighth day the eschar separated from the underlying dermis, taking about half the pigment with it, and, **D.** the appearance of the site 38 days after treatment.

tattoo machine is used. Anesthetic is not necessary if the patient abrades the skin himself, since the salt acts as a local anesthetic.[8] The patient is then instructed to wrap a moist 4x4 gauze sponge impregnated with salt around his index and middle fingers and to begin rubbing the tattoo he wishes to remove. The abrasion continues till the skin becomes "blood" red and appears like good granulation tissue. This usually takes 30 to 40 minutes. At this point, the treated area is covered with antibiotic ointment and a sterile dressing which is left in place for three days.

When a dermabrador or tattoo gun is used, the skin is either superficially abraded or punctured in the desired areas and then covered with a layer of table salt. The insult to the dermis must be very superficial. The mixture of blood and plasma will carry the sodium chloride to the dermis. At this point, when the treated area will look raw but not blood red, it is covered with a layer of salt for four hours. The dressing is then changed and the wound cleaned and redressed with an antibiotic ointment for an additional three days.

On the third postoperative day the treated area is dry and has the appearance of tanned leather. This salted area separates between the seventh and twelfth postoperative days. With eschar separation one may see that about half of the ink has been removed. Still more ink leaves the treated area in exudate while the skin is healing. The abraded area remains erythematous for approximately six weeks and has a tendency to become hyperpigmented if exposed to sunlight. The skin heals quickly and with virtually no scarring. A second treatment can be administered six to eight weeks after the first.

Results

Case 1. A 25-year-old white man who six years earlier had had a multi-colored tattoo professionally applied to his forearm (Figure 1), removed about ninety percent of the tattoo pigment by use of salabrasion for 35 minutes. Forty-eight hours after treatment the skin at the site had taken on the characteristics of tanned leather. Eight days after salabrasion, the eschar had separated, taking with it approximately half of the tattoo pigment. The skin had completely healed by the 38th day. At this time, hair was already growing from the treated area and there was mild hyperpigmentation secondary to sun exposure.

Case 2. The patient, a white man 22 years of age, had had a "homemade" tattoo with india ink applied to his left arm two years before treatment (Figure 2). On instruction, he used salabrasion for 30 minutes on one area of the tattoo. After 21 days the treated area had lost about nine-tenths of its ink content. There was an eczematous eruption at the site, secondary to the antibiotic dressing used.

Case 3. A 24-year-old white man with a professionally applied black ink tattoo that had been on his forearm for five years was treated with a tattoo gun whose needles were set at 1 mm of penetration. The treatment was applied for four or five minutes at the center of the tattoo. The area was then wiped dry and covered with a layer of



Figure 2.—Left, a two-year-old "homemade" india ink tattoo. **Right,** three weeks after the first treatment to the hat area only. The eczematous reaction was secondary to a topical antibiotic.



Figure 3.—Left, a five-year-old professionally applied tattoo, before treatment. **Right,** four weeks after treatment by superficial penetration of the skin with a tattoo gun and topical application of salt at the site of densest pigmentation, the treated area is almost entirely depigmented.

table salt for four hours. The salt was removed and a sterile dressing applied. At the end of four weeks, the center of the flower showed decided loss in pigmentation (Figure 3).

Discussion

How salt acts to remove pigment-impregnated skin is not known. Success may be attributed to the initial tanning which removes the majority of superficial epidermal and dermal pigment, with an increased phagocytic response in macrophages following. At the end of the first week, only about half of pigment is removed with the initial eschar but during the following 14 days additional fading occurs.

Boo-Chai reported that superficial dermabrasion of tattoos creates an inflammatory response and thus promotes the "biologic removal" of pigment through the lymphatics and the sloughing of superficial macrophages.[9] Clabaugh postulated that the pigment-laden phagocytes may become mobile and migrate to the wound surface where they are removed by daily dressing changes.[10] The treatment of tattoos with salt may enhance this phagocytic response.

From a review of the literature it appears that most early techniques owe their success to the inflammatory reaction of salt or a caustic substance. Aetius, in his treatise, directed, "On the sixth, remove the mixture and prick the area with a sharp-pointed instrument, wipe off the blood with a sponge, and powder the punctures with a thin layer of salt."[5] Scutt recently reported on the the Variot method of over tattooing with a 50 percent tannic acid solution.[5] I have used a strong solution of phenol.

In the treatment of 200 tattoos in a two-year period I became dissatisfied with most methods because of the expense in time and money. With superficial dermabrasion, although it has enjoyed great success over the past ten years[1,9-11] there is occasional atrophic scarring or poor result.

In a more recent series I have used salt in treatment by light dermabrasion in ten cases, tattooing in two cases and salabrasion in 13. In all cases there was uniform removal of pigment in the treated areas with virtually no scarring.

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Refer to: Arsenic poisoning—Medical Staff Conference, University of California, San Francisco. Calif Med 118:13-17, Mar 1973

Arsenic Poisoning

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* *The topic for presentation this morning at Medical Grand Rounds will concern itself with arsenic poisoning. The case summary of the patient will be given by Miss Kathy O'Farrell who is a clinical clerk visiting us from the University of West Virginia School of Medicine.*

MISS KATHY O'FARRELL:† This is the second admission for a 38-year-old white man who presented with complaint of numbness and tingling in his hands and feet that had become progressively more severe during the week preceding admission. The patient had been in good health until, about three weeks before admission, he had sudden onset of headaches, abdominal pain, and diarrhea after cleaning an electroplating tank with lye and refilling it with hydrochloric acid and wetting solution. The same evening he began passing dark urine and light-colored stools. Two days later he began to vomit, and anorexia and a low-grade fever developed. These symptoms led to his first admission here. During that admission, the gastrointestinal symptoms improved, but a right lower lobe infiltrate and skin rash developed, as well as tingling in the fingers and toes. Laboratory studies at that time revealed increased values for serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH), blood urea nitrogen (BUN), and creatinine. Urinalysis revealed 1 plus proteinuria and a positive urinary porphyrin screen. Upper gastrointestinal and gallbladder radiographic series were negative, but endoscopy revealed two superficial posterior wall duodenal ulcers. The patient was discharged after one week in hospital. Over the ensuing days, the numbness and tingling in toes and fingers progressed to involve the legs and forearms, and the patient noted difficulty walking. He was readmitted, and when, a day later, the results of the urine heavy metal screen from the first admission became available, they showed a toxic level of arsenic.

On physical examination the patient appeared alert and anxious and was quite unsteady on his feet. Vital signs were normal, as were results of

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Kathy O'Farrell, Clinical Clerk, University of West Virginia School of Medicine.

examination of the head, eyes, ears, neck, chest and heart. The abdomen was tender in all areas and the tip of the spleen was palpable. There was no hyperpigmentation of the skin, hyperkeratotic lesions of the palms, or transverse lines under the fingernails. A resolving rash was present on the chest and upper back. Neurological examination revealed moderate distal weakness of all four limbs, loss of vibratory sensation in both the upper and lower extremities, and loss of pain and touch sensation in the feet. The tendon reflexes were 3 plus in the arms and essentially absent in the legs. The gait was severely ataxic.

Admission laboratory data revealed a hemoglobin of 11.7 grams per 100 ml, hematocrit of 35.1, and normal indices. Platelets numbered 407,000 and white blood cells 2700 per cu mm with 61 percent lymphocytes, 21 percent neutrophils and 9 percent eosinophils. Serum electrolytes were normal, the BUN was 22 mg and the creatinine 1.2 mg per 100 ml. The SGOT was 93 units and the LDH 145. The values for BUN, creatinine, and serum enzymes were less than those during the previous admission. Urinalysis, however, still revealed 1 plus proteinuria and a positive porphyrin screen. The cerebrospinal fluid had a glucose content of 79 and a protein content of 77 mg per 100 ml, and there were 6 lymphocytes per high power field. Analysis of pubic hair for arsenic revealed 3.1 parts per million (normal, 0.3 to 0.5) and the urine contained 0.55 parts per million (normal up to 0.02 parts). Electromyograms were consistent with a polyneuropathy of the dying back type. During the patient's stay in hospital, the leukocyte count dropped to 1,900 per cu mm at one point, with 8 percent neutrophils and 20 percent eosinophils. At the time of discharge, the count was 3,000 per cu mm. Platelets remained within the normal range. Results of liver function tests returned to normal, the right lower lobe infiltrate cleared, and the patient's appetite improved, but he began having frequent leg cramps. British antilewisite (BAL) therapy was not instituted, because of the three-week time lapse since his exposure. Since his discharge [two weeks previously at the time of this presentation] the neurological status has remained essentially unchanged but severe persistent leg cramps have developed that are unresponsive to quinine and prevent his being here today. Analysis of the old and fresh hydrochloric acid solutions and the wetting solutions to which he was exposed revealed trace amounts of arsenic, antimony and phosphate.

DR. SMITH: *Thank you, Miss O'Farrell. This patient was presented to me as an unknown on medical ward rounds. I am told that he represents a classic case of arsenic poisoning. I can assure you that I noted the ill-concealed delight on the faces of the house staff as I went down to crashing defeat trying to tie together porphyria, multiple system disease, leukopenia, and neuropathy, all of which are so typical of this syndrome to those who know it. Fortunately, we have someone here today who is well informed with respect to this syndrome. He is Dr. Arthur Asbury, Vice-chairman of the Department of Neurology and Chief of Neurology at Fort Miley Veterans Administration Hospital, who will tell us how we should go about recognizing this syndrome in the future.*

DR. ASBURY:* Thank you, Dr. Smith. I only hope that I am able to recognize it in the future. I trust that some of the remarks I make this morning will help you do the same. I have seen the patient, who unfortunately cannot be here today. He still has leg cramps, and it was felt inadvisable to ask him to make the trek although he does live in the Bay Area. I shall try to bring him into my discussion at each point along the way so as to pull the case together particularly for those who have seen him on the ward and know him best.

Perspective

I shall start out by giving you some historical perspective of arsenic intoxication. Arsenic is synonymous in the public mind with poison, and actually today the majority of cases of arsenic intoxication are from attempts at homicide or suicide, though some are accidental. Some of them are iatrogenic, especially in less well-developed areas, where arsenic-containing compounds are still used medicinally. For example, Fowler's solution which contains potassium arsenite in rather generous quantities is sometimes used for psoriasis. Arsenic was well known to the ancients in Galenic times and was prescribed mainly in the form of the yellow compound orpiment (arsenous sulfide). It occurs naturally and has been mined for many years as a pyrite mixure. In the Renaissance era, orpiment was used as a poison and particularly by the Borgias, who said they favored it. In my reading about the forensic aspects of arsenic intoxication, I came across an interesting paragraph in a book by a man named John Glaister

*Arthur Asbury, MD, Vice-chairman, Department of Neurology and Chief of Neurology, Fort Miley Veterans Administration Hospital.

who was a forensic pathologist in Scotland (Glaister, J., "The Power of Poison," Cristopher Johnson Publishers, London, 1954, p. 79). He writes as follows:

> About 1659 a wave of suspicious poisoning broke out in Rome when many married men died, and the incidence of young widowhood mounted. The deaths of many of the husbands were closely linked with the fact that they had been peculiarly unaccommodating so far as their wives were concerned. The government on taking a stand and investigating the whole affair, disclosed a nest of young wives directed by an old woman named Spara. This Sicilian, so far as the art of poisoning was concerned, was an apt pupil of an infamous woman called Toffania who sold the poison, although she gave her preparations away without payment to such wives as wished to have other husbands. It is said that Toffania distributed her poison in small glass phials ornamented with the image of a saint. The aqua Toffania was said to be crystallized arsenic. The whole of this coterie of young women was arrested and put to torture. Old Spara and four others were publicly hanged. Toffania lived to a very old age, but finally having been taken from a monastery where she had hidden, was put to torture, confessed her crimes, and was strangled.

So there is an insight into another time, the 17th century. Perhaps when we become concerned with violence in our own age, it is well to reflect back on others.

Systemic Effects of Arsenic Intoxication

Let us now consider the systemic effects of arsenic intoxication. An acute toxic dose of arsenic is approximately 100 mg as arsenous oxide. Patients receiving much more than this are likely to die in the first 12 hours with overwhelming gastroenteritis, cardiac collapse, myocardial failure, and coma, often with convulsions as well. Patients who have had massive doses are probably not salvagable, but fortunately such instances are rarely seen. More common among patients seen in the emergency room is the sub-lethal dose, and usually the clinical story goes something like this. A few hours after an acute single ingestion or exposure to dust, acute and often violent gastroenteritis develops, with severe generalized body and stomach cramps and pernicious vomiting, then rice-water diarrhea. In days gone by, the patients died in the throes of gastroenteritis, but today, with fluid replacement, patients can usually be brought through this stage even though the diagnosis may not be known. Interestingly, arsenous oxide is as radiopaque as barium, and an alert clinician sometimes can make the diagnosis of arsenic ingestion from a plain film of the abdomen taken during the work-up of the gastroenteritis. There is a nice little note in the New England Journal of Medicine in 1962 by Hilfer and Mandel,[1] documenting just such an instance. Over the next day or two, the patients may become icteric and have a greater or lesser degree of hepatic necrosis. In addition, they usually have severe irritation of mucous membranes with a feeling of very tight constriction in the throat, profuse hyperhidrosis, tearing, and increased salivation. In fact, some patients have complained of scalding tears—tears that irritate the skin as they roll down the cheek—as a feature of the increased glandular activity of the mucous membranes. The skin often manifests the effects of arsenic intoxication, and the variety of rashes that have been described are legion. Generally, in acute intoxication, the rash is erythematous and in no way diagnostic of the condition. However, in chronic arsenic intoxication, hyperpigmentation is the rule and often it is attended by keratosis, particularly of the palms and soles, with characteristic cracking and fissuring of the skin. There are many illustrations published in the literature of huge pieces of skin peeling away from the palms in such patients.

Chronic Arsenic Intoxication

The features of chronic arsenic intoxication are beautifully described by Kelynack and his colleagues in an article in the Lancet in 1900.[2] Kelynack, the senior medical registrar at Manchester, awoke to the possibility that the presumed alcoholic peripheral neuritis in a large number of patients they were seeing in Manchester and adjacent towns might in fact be due to arsenic intoxication. In a period of six or eight months they saw several thousand patients, of whom about 70 died. On looking into the matter from the epidemiological standpoint, they found that most of the patients were from the poor working classes and that they drank large quantities of beer. On analysis, the beer was found to contain large quantities of arsenic. The brewers were approached, and when the various ingredients of the beer were analyzed, it turned out that all the invert sugars and dextrose that went into the beer were generously laced with arsenic, apparently derived from the sulfuric acid used to pro-

duce the sugars. In those times the pyrites used in making sulfuric acid contained over 2 percent arsenic. The cutaneous manifestations and the characteristics of the neuropathy are memorably described in the Kelynack paper. In addition to the hepatic necrosis, renal tubular necrosis with acidosis, oliguria, and proteinuria may accompany the initial overwhelming intoxication. Indeed, here in this hospital about two years ago we saw a young man who attempted to kill himself by taking a large dose of an arsenical compound. Very deep jaundice and almost complete renal shutdown developed, and then, during recovery from these conditions, severe neuropathy. Bone marrow depression has been a frequent feature in the cases we have seen here in the last few years. Leukopenia and normochromic anemia are invariably present and are thought to reflect bone marrow depression. I am unable to explain some of the features in our case today. I am unaware of porphyrinuria's having been reported with arsenic intoxication. One would wonder whether or not there was also a component of lead intoxication, in which coproporphyrinuria is an outstanding feature.

Let us now consider the toxicology and the availability of various arsenic compounds[3,4] before we go on to the neurological aspects of arsenical poisoning. Lead, calcium, and magnesium arsenate are the most common arsenicals and they are used primarily as pesticides in sprays of various kinds. Arsine gas, which is produced by reduction of these compounds, is usually an industrial hazard. Another compound that is fairly widely available, especially in the southeastern part of the United States, is copper acetoarsenite. This interesting compound, usually called Paris green, has been widely used as an insecticide on tobacco in North Carolina and Kentucky. I can remember very well having heard as a youth the complaints of tobacco growers about having to dust the tobacco at a certain stage to control worms. Every one hated to use Paris green because they could expect to have gastroenteritis during the night following a day of dusting with it. Why more people did not die or get severe peripheral neuropathy is not known. Paris green is a brilliant green color, and some of its congeners, such as emerald green and Schweinfurt green, were used as dyes in paint and wallpaper until a stop was put to this usage. There was an old wives' tale that it was dangerous to have green wallpaper because it could poison you; indeed the dye did flake and measurable concentrations of arsenic could be measured in the air of such rooms. Fortunately, these compounds are no longer used in dyes. Fowler's solution, as I have already mentioned, is apparently still occasionally used for psoriasis. Cacodylate buffer used in laboratories has a high arsenic content and represents a hazard in the laboratory.

Clinical Neuropathy

Let us now move on to the clinical neuropathy.[5-8] By and large the neuropathy is a late occurrence in the course of acute arsenic intoxication. It usually appears between the seventh and the fourteenth day after a single ingestion. It begins with tingling in the toes and fingers. If it is going to become severe, it will progress over the course of a week or two, plateau, and then take weeks and sometimes months to abate. The degree of recovery depends upon the severity of the neuropathy. Our patient has relatively mild neuropathy from the motor standpoint. He has mild distal weakness in his hands and feet, but is more disturbed by dysesthesia. Almost all patients have such severe hyperpathia in the affected parts that they are unable to tolerate light stroking of the skin or the pressure of bed clothes. This unfortunately may persist for many weeks or months after the intoxication, even when the motor paralysis has completely disappeared. What the factors are that determine whether or not someone will have persisting dysesthesias for many weeks or months is not known. Perhaps at this point I should tell you about another patient whom we saw at the Veterans Administration Hospital two or three years ago in whom another aspect of arsenical neuropathy was represented. The patient was a 50-year-old man who had married some four years previously. About a year after the marriage he began having attacks of gastrointestinal distress that would come and go every month or so. He was admitted two or three times to the Veterans Administration Hospital, but no cause was found for these episodes. He continued to be plagued by recurrent cramps, nausea, vomiting and diarrhea. Then over a period of several months he noticed increasing pigmentation of the the skin and a fluctuating but mild distal symsymmetrical polyneuropathy. We were asked to see him in consultation. We thought that he might have one of those rare neuropathic conditions seen with hemochromatosis, because of the increasing pigmentation and because of the presence of some liver disease. Accordingly, we asked the

house staff to get a serum iron determination immediately and, only as an afterthought, to send off specimens of hair and nail for arsenic analysis. The analysis revealed a 100-fold increase in the arsenic level in the nails and massive quantities in the hair. We asked the patient where he could conceivably have come into contact with arsenic. When he could think of no such exposure, we asked rather directly whether anyone might wish to harm him. He denied this possibility. We then asked if we could speak with his wife. When we did, we found it difficult to meet her eye, as she continually looked away. We told her we were afraid someone was intent on harming her husband, and asked whether she knew who it might be. Later we notified the local police authorities, and since then our patient has been in exemplary health. This is the usual situation. I have seen six patients who had an arsenical neuropathy in the past few years, and in at least four there was homicidal and in one suicidal intent. I have already referred to the latter case.

The patient who was presented today must have suffered an industrial exposure related somehow to the cleaning of the electroplating tank. I must say that I am not a toxicologist and do not know exactly what sequence of events must have taken place in the tank.

With respect to the treatment of arsenic intoxication, recent evidence indicates that there is a very real place for the use of BAL. Most of the literature before 1966 was quite equivocal about the use of this agent. For example, Heyman and his associates[5] concluded that it did not work. However, their patients were seen usually four to six weeks after the acute ingestion. By contrast, Jenkins[6] has shown very nicely that if patients are treated with BAL within the first 18 hours after ingestion, neuropathy can be forestalled. BAL is given by deep intramuscular injection several times in the first 24 hours and then once or twice daily for ten days thereafter. Thus, the early use of BAL is certainly indicated, but once neuropathic symptoms have appeared, there seems little point in subjecting a patient to the discomfort of such treatment.

DR. SMITH: *Thank you, Dr. Asbury.*

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Mesenteric Vascular Insufficiency

Identification and Management

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ALTHOUGH MESENTERIC VASCULAR INSUFFICIENCY may result from a variety of disease processes affecting the venous or arterial circulation of the bowel, it is most often the result of occlusive disease of the large arteries. The incidence of mesenteric vascular insufficiency in the general population is unknown since many patients may be asymptomatic even in the presence of severe obliterative disease of major mesenteric arteries. Even when mesenteric insufficiency does cause symptoms, the diagnosis is easily overlooked because of the lack of objective findings. Most often the patient is not treated for mesenteric ischemia until his condition has become acute, a catastrophic situation associated with extensive gangrene of the bowel and a death rate that has exceeded 80 percent for the past 30 years.[1-3]

Contrary to common belief,[4] mesenteric vascular insufficiency is not an uncommon problem but one that results in at least 1,800 deaths a year in the United States.[5] Nor is the problem of acute mesenteric vascular insufficiency as hopeless as the high mortality might suggest. Many of the diseases that eventually result in mesenteric infarction can be treated successfully by early and appropriate surgical or medical management. For successful treatment, however, it is essential that patients with mesenteric vascular insufficiency be identified—preferably during the chronic stages of their illness, but certainly during the early stages of the acute process. For discussion, mesenteric vascular insufficiency may be classified by etiologic factors.

Classification of Mesenteric Vascular Insufficiency

1. Infarction due to venous thrombosis.
2. Ischemia or infarction due to occlusion or stenosis of major arteries.
 a. chronic occlusion or stenosis.
 b. acute occlusion.
3. Median arcuate ligament syndrome.
4. Ischemia or infarction due to small vessel disease.
5. Ischemia or infarction due to medication.
6. Ischemia or infarction secondary to surgical procedures.

Venous Disease

Etiology and Incidence

The relative contribution of venous disease to the picture of mesenteric vascular insufficiency is difficult to assess since venous thrombosis may lead to arterial thrombosis and vice versa. Various investigators have estimated that between 10 and 33 percent of intestinal infarction is due pri-

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marily to venous disease.[6,7] In approximately 25 percent of patients with mesenteric venous thrombosis no precipitating cause is found.[7] Intra-abdominal sepsis from appendicitis, diverticulitis, pelvic abscess, ulcerative colitis or cholecystitis accounts for the majority of cases of mesenteric venous thrombosis in which a cause is determined. Occasionally, mestenteric venous thrombosis can be accounted for by hypercoagulable states as seen in polycythemia rubra vera,[8] sickle cell anemia or carcinomatosis. Local venous congestion secondary to cirrhosis, portal hypertension, tumor or trauma can also result in mesenteric venous infarction.

Clinical Features

There is some debate in the literature as to whether the onset of signs and symptoms is more rapid in venous or in arterial mesenteric vascular occulusion.[7,9,10] Our experience substantiates that of others[7,9] that although the process of venous thrombosis may occur over several days, the patient usually presents in sudden, acute and severe distress. It is important to realize that acute obstruction of the portal vein or superior mesenteric vein rarely results in infarction in man unless clotting extends to the bowel wall and involves the venous arcades and vasa recta.[7] Moreover, incomplete occlusion of the mesenteric veins (as by tumor mass) is almost always asymptomatic. Mesenteric venous thrombosis usually begins in the smaller veins and extends centrally. If intestinal necrosis does develop from venous thrombosis, the infarction usually involves a shorter segment of bowel than does that which results from acute arterial occlusion.

The primary symptom in mesenteric venous occlusion is abdominal pain. At first the pain is generalized, but later localization over the segment of infarcted bowel occurs. Vomiting is common, as is bloody diarrhea. Shortly thereafter shock supervenes, with evidence of profound hypovolemia and dyhydration. Abdominal guarding is common. The presence of abdominal rigidity and rebound tenderness suggest perforation and peritonitis. Bowel sounds are characteristically hyperactive at first but become hypoactive or absent as necrosis and peritonitis develop. The patient may have the stigmata of the underlying disease process, such as dilated veins in the abdominal wall of the cirrhotic patient.

Laboratory studies reflect the presence of dehydration and sepsis with an elevated hematocrit and leukocytosis. Urinary output is scanty or absent. The lactic dehydrogenase (LDH) and serum glutamic oxalic transaminase (SGOT) and serum am-

ylase are elevated. Unlike the levels seen with acute pancreatitis, the serum amylase may remain persistently elevated for several days. Plain films of the abdomen often reveal dilated, gas-filled loops of the bowel.

Treatment

Surgical resection of involved bowel is the only effective treatment. Vascular reconstruction is not possible because of the pathogenesis of the venous disease. Anticoagulation should be initiated 12 to 24 hours postoperatively. Naitove and Weissman[11] reported a 50 percent mortality without anticoagulation as compared with no postoperative mortality when anticoagulation was instituted following resection.

Chronic Obstruction of Major Arteries

Background

That abdominal pain may be of vascular origin was proposed as early as 1894.[12] The term angina abdominis was introduced by Baccelli at the turn of the century to describe chronic recurrent attacks of abdominal pain due to arteriosclerosis of the mesenteric arteries.[4] Osler and Allbutt, however, disputed this mechanism of abdominal pain. Allbutt believed the abdominal pain to be an aberrant form of angina pectoris while Osler regarded it as but a manifestation of ordinary angina. In 1918 Goodman clearly described an elderly patient with recurring attacks of abdominal angina that responded to dietary restriction, nitroglycerine and amyl nitrite.[4] Multiple reports of this syndrome then followed[13-16] but even as late as 1931 it was not generally accepted that intra-abdominal pain of vascular origin could occur in the absence of gangrene or peritonitis.[17] In 1936 Dunphy commented that it was the lack of postmortem evidence that had prevented acceptance of the fact that occlusive disease of the mesenteric vessels could produce abdominal pain. He studied the histories of 12 patients who had died of mesenteric vascular occlusion. Seven of them had history of chronic recurrent abdominal pain preceding death by weeks, months, or years. Dunphy also observed that the abdominal pain was precipitated by the ingestion of food.[18] In 1957 Mikkelsen coined the term *intestinal angina* and proposed that this syndrome could be cured by elective revascularization of the mesenteric vessels.[19] In 1959 the same investigator reported the first patient to be successfully operated upon electively for correction of mesenteric vascular insufficiency.[20] Even now, 70 years after the initial description of this syndrome, the concept of intestinal angina is not well accepted. As of 1966, Morris could find only 18 cases of elective mesenteric revascularization reported in the literature.[21] He added 31 cases. In 1971 Williams stated that only about a hundred cases of successful elective revascularization of the celiac or mesenteric arteries had been published.[22]

Incidence and Etiology

The cause of intestinal angina is almost invariably arteriosclerotic involvement of the mesenteric arteries although it has also been reported to have been brought about by abnormalities such as isolated celiac arterial compression (median arcuate ligament syndrome), low cardiac output, fibromuscular hyperplasia, aneurysms of the aorta, celiac axis or superior mesenteric arteries, mesenteric arteriovenous fistulae and the postcoarctation syndrome.[22-26] However, arteriosclerotic disease of the mesenteric arteries is an extremely common occurrence. Arteriosclerotic disease of these vessels is by no means an indication that the patient will have intestinal angina. Significant narrowing or occlusion of one or more major mesenteric vessels has been observed at autopsy in from 20 to 50 percent of unselected cases without intestinal infarction.[22,26,27] In only one-third of these patients (at most) had there been symptoms attributable to intestinal angina during life.[26] It has been suggested that the combined cross-sectional diameters of the celiac axis and the superior and inferior mesenteric arteries must be reduced to one-third or less of normal before symptoms of intestinal angina will develop.[28] Even this is speculative since there are multiple reports of patients in whom complete occlusion of both the celiac axis and the superior mesenteric artery was not only compatible with life, but did not result in symptoms of intestinal angina.[29,30] The explanation for this latter observation lies in the ability of the body to establish effective collateral circulation between the three major mesenteric arteries. The gastroduodenal, superior and inferior pancreatoduodenal, middle colic and occasionally the right hepatic artery can become major channels between the branches of the celiac axis and the superior mesenteric artery. Of more significance is a vessel variously known as the meandering mesenteric artery, the central anastomotic artery or the marginal artery of Drummond. This vessel

forms the major collateral circulation between the superior and inferior mesenteric artery. It has been our observation that the presence of this greatly enlarged collateral is a certain indication that there is severe disease in two of the three major mesenteric trunks. Patients who are able to develop such collaterals are often asymptomatic. Conversely, when the main mesenteric trunks are severely compromised, inability to establish these collaterals often results in intestinal angina or frank gangrene of the bowel.

It would be wrong to conclude from the statements above that pronounced stenosis or occlusion of the major mesenteric vessels is harmless whether intestinal angina is present or not. There can be little doubt that the prognosis is poor for patients with intestinal angina.

Several studies have indicated that symptoms of mesenteric vascular insufficiency will have been present for months or even years in 30 to 50 percent of patients who die of massive intestinal gangrene secondary to arteriosclerotic occlusion of the mesenteric vessels.[18,31,32] The existence of this prodromal period in many patients provides an opportunity to prevent mesenteric infarcation if the symptoms are recognized and appropriate studies and treatment are carried out.

Clinical Features

Intestinal angina is a manifestation of intermittent gastrointestinal ischemia. As such, the outstanding symptom is abdominal pain which, like the pain of angina pectoris or intermittent claudication, is related to effort or the workload necessary for digestion. Characteristically, the pain of intestinal angina begins 15 to 20 minutes after ingestion of food and persists for one to three hours. The patient usually describes the pain as crampy and located in the epigastrium or periumbilical region. It may vary considerably in intensity, ranging from a vague ache to severe distress. As the underlying process progresses, the pain increases in intensity and occurs earlier after smaller meals. The development of continuous abdominal pain instead of the characteristic intermittent postprandial pain is ominous since it heralds intestinal infarction. At first the pain may be relieved by heat, reducing the size of meals, changes in position or the administration of anticholinergics or nitroglycerine. Understandably, a patient with intestinal angina soon learns that reducing the quantity of food ingested will prevent or lessen his discomfort. As a result, weight loss is typical although not invariably present. Approximately half of the patients complain of constipation and distension but others report diarrhea or alternating diarrhea and constipation.

It is characteristic of intestinal angina that there are few if any physical findings in the abdomen, even during an episode of severe pain. There is often evidence of weight loss and of arteriosclerotic disease elsewhere. An abdominal bruit near the umbilicus is frequently present in these patients and should alert one to the possibility of intestinal angina. However, the presence of an abdominal bruit is not diagnostic of abdominal angina since a bruit may occur with disease of other vessels as well as the mesenteric arteries. Abdominal distension may be present during an attack of pain but abdominal tenderness is uncommon. Abdominal rigidity, guarding or rebound tenderness do not occur in the chronic form of intestinal angina. Bowel sounds may be hyperactive during the early phase of symptoms but are usually normal in intensity and frequency even when intestinal distension is apparent on a plain film of the abdomen.

Routine laboratory studies and conventional radiographic examinations usually reveal no abnormalities. Malabsorption can sometimes be demonstrated by studies of fecal fat and nitrogen as well as by d-xylose, triolein I-131 and oleic acid I-131 tests but the passing of fatty stools is uncommon. Occult blood in the stool is a common finding in these patients but frank melena occurs only after infarction of the bowel. Gastrointestinal x-ray films are characteristically negative but sometimes reveal evidence of decreased intestinal motility—puddling of barium in the small bowel, with flocculation or segmentation.[12,19,21,22] "Fingerprinting" of the bowel margins has also been described.

Abdominal aortography with both anterior-posterior and lateral views is the essential diagnostic procedure when a diagnosis of intestinal angina is suspected. Anterior-posterior views will demonstrate the origin of the inferior mesenteric artery and, when they are present, collateral vessels notably the central anastomotic artery to which we referred earlier. Lateral views are essential to examine the origins of the celiac and superior mesenteric arteries since these vessels arise from the aorta anteriorly and are partially obscured in the anterior-posterior views. Visualization of the first 1 to 2 cm of the superior mesenteric artery

is of particular importance since obstruction or narrowing of this vessel is present in 90 percent of patients with vascular disease of the intestine.[33] With the possible exception of the median arcuate ligament syndrome (mentioned elsewhere herein) chronic obstruction of only one of the mesenteric vessels is rarely if ever sufficient to cause intestinal angina. Occlusion or severe stenosis of the superior mesenteric artery together with disease of at least one of the remaining two mesenteric arteries is the characteristic finding in patients with intestinal angina.[10] The celiac axis and the superior mesenteric artery are the two vessels most frequently involved in the arteriosclerotic process leading to intestinal angina. Selective visceral angiography, if available, can help in determining the direction of flow in collateral vessels and in delineating distal arterial lesions. It should be emphasized, however, that intestinal angina is most often the result of proximal disease of the mesenteric vessels and rarely is due to arterial disease distal to the first 2 cm of these vessels.[9,19,31]

Diagnosis and Treatment

Medical management of intestinal angina consists of dietary measures such as a bland diet and small feedings, use of analgesics, externally applied heat, rest after meals, anticholinergics, vasodilators such as nitroglycerin, and treatment of coexisting diseases such as congestive heart failure and arryhthmias that may aggravate or even precipitate intestinal angina. For the most part, these measures do not relieve the patient's symptoms for any length of time nor do they prevent catastrophic progression to acute mesenteric infarction with its associated mortality. In recent years few would challenge the belief that once the diagnosis is established, intestinal angina is best treated by elective vascular reconstruction. Nevertheless, the vast majority of patients with mesenteric vascular insufficiency are not operated upon until massive intestinal infarction has occurred. The major reason for the infrequency with which elective revascularization of the bowel is performed is the difficulty encountered in establishing a diagnosis of intestinal ischemia. We believe that the diagnosis of intestinal angina should be considered as a possibility in every patient

(1) who describes the characteristic symptoms of postprandial abdominal pain, weight loss and change in bowel habits, and

(2) in whom a midabdominal bruit is heard, and

(3) in whom conventional diagnostic studies do not establish disease of the gastrointestinal or biliary tract that would explain his symptomatology.

Such patients should be studied angiographically. If stenosis greater than 50 percent or occlusion of two or more of the mesenteric vessels is demonstrated, the diagnosis should be considered to be intestinal angina and elective revascularization of the bowel should be performed.

Thromboendarterectomy, bypass grafting and reimplantation are the procedures employed for revascularization of the bowel. Preference for one or another of these techniques depends not only upon the extent and location of the lesion as determined by angiography, but also upon the anatomic situation at the time of operation and the preference of the surgeon. We have found that endarterectomy of the stenotic superior mesenteric artery can often be accomplished readily although we have also employed bypass grafting of the superior mesenteric artery in obese patients or in patients with more extensive lesions. Because of its location high in the abdomen, and because the arteriosclerotic disease is at its origin, endarterectomy of the celiac axis is more difficult than endarterectomy of the superior mesenteric artery. Therefore, bypass grafting is the procedure of choice for revascularization of the celiac axis.

Our experience with elective revascularization of the inferior mesenteric artery has been limited to patients in whom the primary operation was aorto-iliac reconstruction or resection of an abdominal aortic aneurysm. In about 30 percent of these patients the inferior mesenteric artery is patent and occasionally constitutes a major collateral to the bowel or lower extremities. In this situation we prefer endarterectomy of the orifice of the inferior mesenteric artery (IMA) if the primary procedure is aorto-iliac reconstruction or reimplantation of a button of aorta bearing the IMA if aortic resection is to be performed.

We prefer the use of autogenous vein grafts rather than synthetic grafts when bypassing mesenteric arterial blocks. In the presence of two or three severely compromised mesenteric arteries we usually employ two grafts although we realize that successful revascularization of only one of the three major mesenteric vessels may be sufficient to restore adequate hemodynamics to the intestinal circulation. Severity of stenosis in a given mesenteric vessel is determined at the time

of operation by measuring the pressure gradient between the aorta and the vessel distal to the lesion. When revascularization is performed, it is essential that existing collaterals be preserved since they constitute an important route for increased blood flow to the bowel and, in the case of graft failure, provide insurance against infarction of the bowel.

Results of elective revascularization of the bowel have been good. In several reported series pain was relieved in more than 90 percent of the patients. Malabsorption, when present, improved in at least 75 percent of patients.[22] Operative mortality has been low. In two series totalling 49 patients, and in our smaller series of six patients, there were no postoperative deaths if intestinal revascularization was the primary operative procedure.[21,29] These reports are in striking contrast to the 85 to 90 percent operative mortality that has resulted when treatment was delayed until mesenteric infarction occurred.

Acute Occlusion of Major Mesenteric Arteries

Background

Extensive gangrene of the small bowel and colon is usually the result of acute occlusion of the superior mesenteric artery. The first such case was reported in 1843 by Tiedemann,[34] and the first successful bowel resection for the condition was accomplished in 1895 by Elliot.[35] The persistently high mortality of this disease led Ryvlin to propose in 1943 that emergency mesenteric embolectomy be performed in these patients.[36] Klass[37] and Stewart[38] were apparently the first to actually perform embolectomy of the superior mesenteric artery. Since that time many investigators have written on the subject of intestinal infarction secondary to mesenteric arterial occlusion. Nevertheless, it is important to note that as late as 1964 reports of successful vascular operations for acute mesenteric arterial occlusion were infrequent.[31] The mortality of this disease continues to exceed 80 percent.

Incidence and Etiology

Acute occlusion of the superior mesenteric artery is not uncommon. In 1964 Marston reported that this disease was responsible for two of every thousand general surgical admissions to hospitals in the United States.[3] Later he reported that there were at least 1,800 deaths from mesenteric infarction in the United States in 1967.[5] The true incidence of this disease is probably even higher since intestinal infarction is not infrequently discovered at autopsy in patients dying of primary diseases elsewhere in the body. In this regard, it is important to realize that about 20 percent of patients with extensive ischemic necrosis of the intestine will develop gangrene in the absence of occlusion of a major mesenteric vessel. The underlying cause in this situation is reduced cardiac output and peripheral blood flow, although atherosclerotic narrowing of the mesenteric vessels is commonly present in these patients. Congestive heart failure, hypovolemic shock, septicemia, cardiac arrhythmias, severe aortic stenosis and the administration of vasopressors have each been described as the precipitating factor in the development of nonocclusive intestinal ischemia and necrosis in these patients.[6,31]

When intestinal gangrene results from acute occlusion of a major vessel, the superior mesenteric artery is almost invariably the vessel involved. Intestinal gangrene rarely occurs following acute occlusion of either the celiac axis or the inferior mesenteric artery unless there is disease in the superior mesenteric artery as well.[10] Thrombosis secondary to atherosclerosis is the cause of acute occlusion in 40 to 60 percent of patients while embolic occlusion is the cause in approximately 40 percent of patients. Because of the angle of its takeoff, the SMA is particularly vulnerable to lodgement of emboli. Approximately 6 percent of all peripheral emboli lodge in it.[31] The emboli are commonly cardiac in origin with atrial fibrillation, mitral stenosis, myocardial infarction and subacute bacterial endocarditis as the underlying cardiac diagnoses. Rarely, the emboli originate from arteriosclerotic aortic plaques. Thrombotic occlusion of the SMA does not occur in the absence of preexisting atherosclerotic narrowing of that vessel. Cardiac decompensation may precipitate thrombosis but approximately 50 percent of patients with atherosclerotic thrombosis of the SMA have no previous cardiac history.

Clinical Features

The traditional belief is that patients suffering acute mesenteric arterial occlusion present as a catastrophic abdominal emergency.[1-5] More commonly, however, the patient is symptomatic for many hours or even several weeks before the signs of peritonitis or cardiovascular collapse supervene. Indeed, Mavor found that 70 percent of his pa-

tients were symptomatic for 12 hours or longer before admission to hospital; 40 percent had been symptomatic for more than two days, and 20 percent for more than a week, before admission. Thus, there is usually time to suspect and confirm the diagnosis as well as to institute appropriate therapy. Unfortunately, the same study revealed that more than 50 percent of the patients who had acute superior mesenteric arterial occlusion were hospitalized with abdominal pain from 12 hours to more than seven days before the diagnosis was suspected strongly enough to perform operation.[1] It has been our experience that the diagnosis of acute mesenteric arterial occlusion is difficult to establish, not because the patient presents with a catastrophic illness, but because he presents with deceptively mild signs and symptoms that do not arouse suspicion of vascular impairment of the bowel.

Abdominal pain is always present in these patients. The character of the pain, however, is variable in intensity and location. Typically, the pain is poorly localized and, when the patient is first seen, is not of great intensity, thus suggesting a minor gastrointestinal disturbance. Vomiting occurs in about 30 percent of the patients, bloody diarrhea in about 20 percent. Initially, examination of the abdomen is deceptively benign. There is no distension, only mild, diffuse tenderness and no signs of peritoneal irritation. Bowel sounds are present but may be slightly hypoactive. Later, however, the abdomen becomes distended and silent. Palpation of the abdomen at this stage reveals a characteristic "doughiness" with poorly localized tenderness. Diffuse rebound tenderness and tympany may be present. The presence of these latter findings in a cardiac patient with atrial fibrillation should strongly suggest the diagnosis of mesenteric infarction. It is not until necrosis proceeds to involve the entire bowel wall that the signs of generalized peritonitis and cardiovascular collapse develop.

In general, laboratory findings are non-specific and serve only to confirm the state of hydration or extracellular fluid loss. A possible exception is the leukocyte count which is characteristically high early in the course of symptoms at a time when physical findings are relatively benign. Plain films of the abdomen reveal gaseous distension of the bowel with edema of the bowel wall. The generalized and diffuse nature of this distension should alert one to the possibility of vascular compromise of the bowel. The presence of gas in the mesenteric veins is a preterminal finding.[5] Peritoneal tap or lavage may aid in establishing the diagnosis. Recovery of cloudy, reddish-brown fluid with a feculent odor is diagnostic of intestinal necrosis. Unfortunately, this is also indicative of an advanced stage of the disease.

Aortography with anterior-posterior and lateral views (as described under the section dealing with chronic intestinal ischemia) is, in our opinion, an essential diagnostic aid when acute mesenteric arterial occlusion is suspected. If such a test is to be of value, however, it must be performed early in the course of symptoms. Delaying this examination until signs of peritonitis have developed is of little help, since the need to explore the abdomen will already be evident at that time and the chance of reversing the ischemic process will almost certainly have been lost.

Treatment

Before discussing the treatment of acute mesenteric infarction, it is appropriate to mention the importance of prevention of this catastrophic illness. Approximately 30 percent of patients in whom acute mesenteric infarction develops secondary to occlusion of the superior mesenteric artery will have had symptoms of intestinal angina for weeks, months or years before the acute episode. Recognition and treatment of this problem during the chronic stage would obviously greatly lessen mortality from the acute episode. Moreover, in about 20 percent of patients in whom mesenteric infarction develops, the cause is not occlusion of an arteriosclerotic superior mesenteric artery, but rather the effects of cardiovascular disease elsewhere. Thus, earlier recognition and treatment of the underlying diseases should significantly decrease the incidence of intestinal infarction in patients with congestive heart failure, aortic stenosis, thromboembolic phenomena, myocardial infarction, atrial fibrillation, mitral stenosis or bacterial endocarditis.

Once the diagnosis of acute mesenteric infarction is strongly considered, surgical exploration is indicated as an emergency measure. The proper operative procedure, however, cannot be determined without exploration. In a few patients, embolectomy of the superior mesenteric artery may be possible and may be the only procedure necessary. More likely, however, some of the small bowel and colon will be frankly gangrenous while the viability of the remaining bowel will be questionable. In this situation it is our belief that

revascularization of the bowel should be brought about by embolectomy, thromboendarterectomy or bypass grafting of the superior mesenteric artery. Obviously, clearly gangrenous bowel must be resected. If the remaining bowel is of questionable viability, we have then added periarterial sympathectomy by dividing the nerve fibers about the origins of the superior mesenteric artery and the celiac axis. Experimentally, the latter procedure significantly increases mesenteric blood flow.[39] On occasion we have re-explored 12 to 24 hours later if the patient's condition permits reoperation and there is serious concern for viability of the remaining bowel.

Since the major cause of death in these patients is septicemia, broad spectrum antibiotics are indicated before, during and after operation. Corticosteroids in pharmacologic dosage—for example 200 to 400 mg of dexamethasone—may be indicated to combat gram-negative septicemia and shock. Massive replacement of blood volume and extracellular fluid volume may be necessary after operation, particularly if a revascularization procedure has been preformed. Acidosis and hyperkalemia are frequently observed in these patients and must be corrected, particularly in the presence of myocardial ischemia or decompensation. Postoperative monitoring of blood gases is advisable since the majority of these patients will require ventilatory support. The most significant adjunct to surgical treatment, however, is early recognition of the disease entity and prompt surgical exploration. Once signs of peritonitis or shock have developed, death is almost certain regardless of the treatment.

Median Arcuate Ligament Syndrome

Incidence and Etiology

It is generally believed that there must be chronic occlusion of at least two of the mesenteric arteries to produce the symptoms of intestinal angina. In 1965, however, Dunbar reported 13 cases in which partial occlusion of only one main visceral artery caused intestinal angina. In these cases the celiac artery was compressed by fibers of the median arcuate ligament of the diaphragm. All the patients were relieved of symptoms by division of the median arcuate ligament. Other investigators have since reported similar cases.[24,41-43] Nevertheless, the existence of this syndrome has been challenged by some observers,[44] who point out that narrowing of the celiac axis by the median arcuate ligament is a common anatomical variation affecting from 20 to 35 percent of asymptomatic persons.[44-46] It has also been proposed that the relief of symptoms following division of the median arcuate ligament is due to the division of the celiac ganglion and nerves rather than to division of the diaphragmatic fibers.[24,47-49] Thus, the cause of this syndrome and even its existence are in dispute. The incidence of this variation of intestinal angina is also unknown. Suffice it to say that surgical treatment of the median arcuate ligament syndrome has been reported in fewer than 50 patients.

Clinical Features

In Dunbar's report, patients afflicted by the median arcuate ligament syndrome were younger (average age 34.5 years) than the typical patient with vascular disease. Most were women. Subsequent reports tend to substantiate these initial observations. The characteristic symptoms resemble those of intestinal angina and consist of episodic, often severe, cramping upper abdominal pain, usually occurring soon after eating. Sometimes there is associated diarrhea, epigastric fullness and nausea. In most patients an epigastric bruit is audible. There are no other characteristic physical findings. Except for those observed by aortography, there are no abnormalities apparent by laboratory or radiologic investigation. Mesenteric infarction has not been reported as a consequence of this syndrome. Diagnosis depends upon demonstration by lateral aortography of a compressed and stenotic celiac axis. Typically, the origin of the celiac axis is normal but a short distance beyond the origin of the celiac axis a severe constriction can be demonstrated, followed by poststenotic dilatation. The superior and inferior mesenteric arteries are found to be widely patent.

Treatment

If one believes in the existence of this syndrome, then the presence of persistent severe symptoms is indication for surgical therapy. The usual procedure is division of the fibrous bands of the median arcuate ligament and freeing of the celiac axis. On the basis of our experimental studies[24] as well as those of others[49] we would add dissection and division of the neural structures about the celiac axis.

In some patients there is an intrinsic "hourglass" lesion of the celiac artery as well as extrinsic compression. In others, arteriosclerotic nar-

rowing of the celiac axis is present in addition to the obstructing diaphragmatic fibers. In all of these patients it is important that pressure gradients be recorded across the stenotic lesion. If a pressure gradient persists after the celiac artery has been dissected free, the intrinsic stenosis should also be corrected by resection and reanastomosis, endarterectomy, patch graft angioplasty or bypass grafting. Failure to relieve a persistent gradient may result in persistent symptoms.

The results of operation for this syndrome are good. In a total of 43 such cases reported in the literature, there were no operative deaths and relief of symptoms occurred in all but two patients.[24,40,50,51] Both of these patients had radiologically proven residual defects in the celiac artery postoperatively.

Intestinal Ischemia Due to Small Vessel Disease

General Considerations

Although we have emphasized in preceding sections that the most common cause of mesenteric arterial insufficiency is obstruction of large vessels secondary to cardiac disease or atherosclerosis, it is important to realize that primary disease of small arteries may also produce intestinal ischemia and, on occasion, may aggravate the effects of large vessel disease. Degenerative disease of the small vessels of the bowel has been reported to occur in the absence of disease in the major mesenteric arteries[26] but the role of these lesions in the production of symptoms of mesenteric vascular insufficiency is not clear. Certain of the inflammatory diseases of the small vessels, however, can produce symptoms of intestinal angina and on occasion have been responsible for fatal hemorrhage, mesenteric infarction, perforation and peritonitis.[52] Feller et al estimate that vasculitis is responsible for three percent or less of cases of mesenteric infarction.[26] More commonly, bowel lesions secondary to arteritis are small and do not require surgical operation.

Polyarteritis Nodosa

Abdominal pain occurs in 65 percent of these patients, 70 percent of whom are male. The pain is typically vague, persistent and poorly localized but may be severe. Mesenteric infarction, perforation and peritonitis occur but are rare. Polyarteritis usually involves the small vessels but has been reported to involve major mesenteric arteries with occlusion of these vessels. At the Mayo Clinic, polyarteritis was responsible for three of 60 cases of mesenteric arterial occlusion.[52] We have observed two patients in whom polyarteritis was responsible for extensive necrosis of the bowel, esophagus and biliary tree. Since steroids are often employed in this disease, physicians must be alert to the possibility that signs of intra-abdominal inflammation, mesenteric infarction or peritonitis may be masked.

Systemic Lupus Erythematosus

As many as 40 percent of these patients complain of abdominal pain so severe that at times "surgical abdomen" is suspected. Abdominal tenderness and bloody diarrhea are not uncommon. Abdominal distension with widely dilated loops of small bowel visible on x-ray studies occurs less commonly. Steroid therapy will usually produce dramatic improvement in the abdominal symptoms although intestinal necrosis with perforation has been reported in patients receiving steroids. Eighty-five percent of patients are females, usually young adults.

Post-coarctation Syndrome

Acute mesenteric arteritis following resection of a thoracic aortic coarctation haas been reported to occur in almost 20 percent of patients surviving operation.[26] Almost all patients are males who have undergone correction of a very narrow coarctation. Symptoms of ischemia of the branches of the superior mesenteric artery characteristically develop after the third postoperative day. Most patients recover spontaneously within two or three weeks. This complication of operation for coarctation can be prevented if the postoperative blood pressure is not allowed to exceed normal levels. If arterial hypertension develops following resection of an aortic coarctation, treatment with blocking agents such as chlorpromazine should be employed to restore the arterial pressure to normal levels.

Buerger's Disease (Thromboangiitis Obliterans)

In 1966, Rob reported a single patient with Buerger's disease who had "cramp-like, spasmodic, central abdominal pain associated with attacks of diarrhea and weight loss"—that is, the typical symptoms of intestinal angina. Arteriograms revealed no abnormalities of the celiac or mesenteric arteries. Exploration revealed a localized segment of ischemic small bowel. Examina-

tion of the resected specimen confirmed the presence of thromboangiitis obliterans.[29] A few additional cases have been reported in which occlusive disease of the mesenteric vessels was attributed to thromboangiitis obliterans, although the lesions were not convincingly those of Buerger's disease.[54] At best, significant visceral involvement by thromboangiitis obliterans seems to be a rare entity. It does appear, however, that the visceral arteries of patients with thromboangiitis obliterans are more than normally susceptible to atherosclerotic and thrombotic occlusion.[54]

Ischemia or Infarction due to Medication

In the section dealing with acute mesenteric arterial occlusion it was noted that about 20 percent of patients who develop extensive mesenteric infarction do so in the absence of demonstrable embolic or thrombotic occlusion of major mesenteric vessels. Most of these patients have pre-existing mesenteric vascular disease complicated by a sustained reduction in cardiac output, most often due to intrinsic cardiac disease. However, it has also been reported that both arterial and venous mesenteric vascular insufficiency can be precipitated by the administration of a variety of medications. Again, most of these patients have underlying arteriosclerotic mesenteric and cardiac disease. The consequences of mesenteric vascular insufficiency secondary to medication range from unexplained episodes of abdominal pain to localized intestinal strictures to extensive and fatal intestinal necrosis.

Digitalis Preparations

It has been known for some years that vigorous digitalis therapy can result in non-occlusive intestinal infarction.[55] Digoxin in particular has been shown to intensify vasoconstriction in the splanchnic circulation.[56] Most of the patients are in congestive heart failure, of course. Clinical manifestations of the intestinal ischemia include abdominal pain, mild tenderness to palpation, diminished bowel sounds, melena and bloody diarrhea—the typical signs and symptoms of acute mesenteric infarction. This complication of digitalis therapy is almost invariably fatal, although therapy with glucagon, epidural block, celiac ganglionic blockade and/or antibiotics has been proposed.[6,56] Postmortem examination usually reveals submucosal hemorrhage with non-inflammatory necrosis of the bowel.

Vasopressors

Normally the splanchnic blood flow accounts about 20 percent of the cardiac output. The volume and distribution of intestinal blood flow is highly variable, however, and is dependent upon cardiac output, blood volume, blood pressure, post-cibal status, circulatory demands elsewhere in the body and multiple humoral and nervous responses. Moreover, circulation to the intestinal tract is often the donor when blood supply to other areas must be preserved. Although relative intestinal ischemia is usually well tolerated, reduction of mesenteric blood flow in patients with preexisting compromise of the intestinal circulation may produce intestinal angina or even frank gangrene of the bowel. Since agents such as vasopressin, epinephrine, norepinephrine, angiotensin, preparations of ergot or amphetamines produce severe vasoconstriction of the mesenteric vascular bed, their use in patients suspected of having mesenteric vascular disease must be avoided. This kind of "supportive" treatment is ill-advised in these patients.

Oral Contraceptives

The occurrence of thrombo-embolic episodes in women taking oral contraceptives is well known. Not so well known is that mesenteric vascular changes with abdominal pain can also occur in these patients. Martel et al[57] reported the case of a 22-year-old woman in whom cramping abdominal pain, nausea, vomiting and diarrhea developed after she began taking a progestational agent. Resection of a jejunal stricture was eventually necessary. Pathological examination revealed intimal vascular prolifieration and thrombosis in the intramural and mesenteric vessels. The authors cited five additional cases and concluded with the recommendation that the onset of abdominal pain in women in any age group is a definite indication for cessation of oral contraceptive agents.[57]

Ischemia or Infarction Secondary to Surgical Procedures

It is well recognized that circulation to the small or large bowel may be impaired during abdominal operations, particularly when extensive dissection is necessary in the region of the pancreas or the base of the small bowel mesentery. Should the intestinal circulation be compromised during these procedures, the fact is readily appreciated and revascularization or resection of the bowel can be

accomplished. There are two specific situations, however, in which impairment of the intestinal circulation may not be recognized either at the time of operation or in the immediate postoperative period. In the first situation sacrifice of the inferior mesenteric artery results in ischemia and/or infarction of the left colon and, rarely, the small bowel. In the other, reconstruction of disease in the aortoiliac vessels causes "stealing" of blood from stenotic or occluded mesenteric arteries that in turn produces intestinal angina or mesenteric infarction.

During resection or reconstruction of the abdominal aorta, it is frequently necessary to sacrifice the inferior mesenteric artery. With few exceptions, ligation of this vessel produces no sequelae even when it is patent. Approximately one percent of the time, however, sacrifice of the inferior mesenteric artery will result in ischemia or gangrene of the left colon.[58] In these patients, there is inadequate collateral circulation to the left colon. On infrequent occasions, the inferior mesenteric artery may be the major blood supply to the small bowel as well (via the marginal artery). Sacrifice of the inferior mesenteric artery in these patients can cause extensive gangrene of the small bowel as well as the colon. Visualization of an enlarged marginal artery by aortography should alert the surgeon to these possibilities, as should discovery of a greatly enlarged inferior mesenteric artery at the time of operation. In either of these situations reimplantation of the inferior mesenteric artery into the aorta or prosthetic graft will avoid the problems of ischemic bowel. If the significance of the enlarged IMA is overlooked and ischemia or necrosis of the bowel develops postoperatively, establishing the diagnosis can be extremely difficult since abdominal pain, the constant symptom of the ischemic bowel, is already present. Should bloody diarrhea develop early after aortoiliac operation, the possibility of ischemic bowel must be strongly considered and reexploration undertaken unless another, non-surgical explanation for the bloody diarrhea can be established.

"Aortoiliac steal" occurs as the result of redistribution of cardiac output into the previously ischemic extremities.[59] If the patient cannot meet the new demands for circulation, blood flow is "stolen" from the mesenteric circulation. Blood is more likely to be diverted from the intestinal circulation if the mesenteric vessels are diseased, if the cardiac output is relatively fixed, or if lumbar sympathectomy is performed together with the aortoiliac reconstruction. "Aortoiliac steal" may manifest itself as intestinal angina or as acute mesenteric infarction. The problem can be avoided by revascularizing stenotic or occluded mesenteric vessels at the time of aortoiliac reconstruction. For this reason, we believe that the mesenteric circulation should be visualized by anterior-posterior and lateral aortography in every patient before aortoiliac reconstruction.

Summary

From multiple clinical and pathological studies it is apparent that severe arteriosclerotic involvement of the mesenteric vessels is by no means uncommon, nor is death as a direct consequence of mesenteric vascular disease. The presence of unexplained, recurrent postprandial pain associated with diarrhea and weight loss should alert the physician to a possible diagnosis of intestinal angina, the chronic form of mesenteric vascular insufficiency. This symptom complex should not be lightly considered since, untreated, it characteristically progresses over a period of days, months or even years with the constant threat of extensive mesenteric infarction and its attendant 80 percent or greater mortality.

Intestinal angina can be treated successfully and at low risk provided the diagnosis is considered. Abdominal angiography with anterior-posterior and lateral views is an essential part of the diagnostic work-up. Surgical correction of the diseased vessels by endarterectomy or bypass grafting will relieve symptoms in more than 90 percent of patients.

Acute mesenteric infarction is the result of venous disease in from 10 to 33 percent of patients, with arterial disease responsible for the remainder. Cardiac disease and arteriosclerosis account for 80 percent of the etiologic factors in acute arterial occlusion. The high mortality associated with acute mesenteric arterial infarction has not significantly improved in 30 years. A diagnosis of acute mesenteric infarction should be strongly considered in an elderly patient who presents in atrial fibrillation with diffuse, poorly localized abdominal pain, abdominal distension without rigidity, absence of bowel sounds and evidence of diffuse arteriosclerotic cardiovascular disease. Awareness of the entity, early diagnosis, proper management of low flow states and early operation should considerably improve mortality statistics. Detection and treatment of these pa-

tients during the chronic or prodromal stages of their mesenteric vascular insufficiency should further lower mortality.

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Important Advances in Clinical Medicine

Epitomes of Progress—Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Orthopedics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Sickle Cell Disease in Orthopedics

SKELETAL ABNORMALITIES occur in patients with sickle cell anemia and its genetic variants because of abnormal circulating hemoglobin S. The orthopedist must learn both the orthopedic and hematological aspects of diagnosis and treatment of this disease complex.

The genetic variants (SC disease, S-thalassemia and sickle cell trait) affect a significant proportion of black people. Homoxygous (SS) sickle cell anemia becomes obvious with severe symptoms in early childhood.

The diagnosis of a variant is difficult unless suspected. Any black patient with an undiagnosed skeletal abnormality, especially avascular necrosis of bone or an atypical bone infection, should have hemoglobin electrophoresis. Symptoms in the variant form may be absent or mild and life expectancy may be normal. Symptoms begin later in life and only 50 to 60 percent of the patients have bone changes.

Avascular necrosis and bone infection are two of the most serious complications. Femoral head necrosis results often in bony collapse, although in younger patients, complete reconstitution of the femoral head may occur with a non-weight-bearing Legg-Perthes program. Some patients with homozygous disease (SS) have severe hip destruction, but may have minimal symptoms, probably because their general disease severely restricts their activities.

Surgical reconstruction of the hip may include varus osteotomy, fusion or arthroplasty. The necrotic humeral head may be bone grafted or a Neer prosthesis may help relieve pain.

The most common bacteria affecting bone is staphylococcus, but the Salmonella species and E. coli may also cause osteomyelitis.

The orthopedic surgeon should work closely with the anesthesiologist and hematologist in the management of these patients.

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Engh CA, Hughes JL, et al: Osteomyelitis in the patient with sickle cell disease. Diagnosis and management. J Bone Joint Surg 53:1-15, Jan 1971

Fasciotomy for Swollen Limbs

THE USE OF FASCIOTOMY for decompressing the osteofascial compartments of the extremities following arterial trauma and its subsequent repair has been known to vascular surgeons since the days of World War II when arterial repairs became a surgical feasibility. This became emphasized again with the Korean conflict and has become a basic surgical tenet. The need for fascial release of the ischemic muscular compartment is also well known to orthopedists. Surgeons with military experience have seen extremities with successful arterial repairs lost because of compartmental necrosis where appropriate fasciotomy was not carried out. Although some argue that not all repaired arterial trauma requires fasciotomy, there is uniform agreement that arterial trauma with delay of more than ten to twelve hours before repair is an absolute indication for osteofascial decompression.

In addition to fasciotomy for vascular embarrassment due to vessel trauma, the procedure is also recognized as an important part of the management of severely comminuted fractures with associated soft tissue injury and compartmental swelling. The iatrogenically produced compartmental swelling following a blind nailing of tibias and the indiscriminate use of Bryant's traction are less known reasons for fascial release of the leg. The forearm fasciotomy for Volkmann's ischemia is well known. Fasciotomy for venous compression problems encountered in drug addicts who have lain comatose on an extremity for a prolonged period are well recognized, as is the need for fascial release in the "crush syndromes." The swollen limb following snake-bite, and also following the paint-gun injury, often calls for fascial release.

The spontaneous onset of the acute anterior compartment syndrome following strenuous sports activity or marching demands urgent fascial decompression to prevent irreparable neuromuscular injury.

PAUL H. BROADLEY, MD

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Knee-Joint Replacement

ALTHOUGH EARLY RESULTS of knee-joint replacement are promising, they suffer by comparison with results of total hip-joint replacement, both as to postoperative morbidity and to relief of pain. Although the immediate serious complication rate does not appear to be higher, there is justifiable concern about long-term joint stability, prosthetic fixation within bone, and wearability.

The two basic types of tibiofemoral knee-joint replacements may be classified as hinged (constrained) and condylar (non-constrained). Neither is truly a total knee-joint replacement, however, since the patella, often also involved with arthritis, is not replaced. The early all-metal hinge units of Walldius have undergone extensive changes in design and materials since they were introduced in the 1950's. These joints rely on intramedullary prongs that extend into the femur and tibia for fixation. The units are rather heavy and bulky and, when implanted as press-fit devices, tend to loosen in bone. Some surgeons have utilized methyl methacrylate, used so successfully in hip-joint replacements, as an adjunct to fixation; however, despite more rigid immediate fixation, this tendency to loosening may still occur, particularly in patients with osteoporosis. Nevertheless, substantial relief of pain, often with improved function, is a reasonable goal for the severely disabled arthritic patient with considerable built-in restraint. These joints are not intended to withstand vigorous activity. At present, hinge units are indicated primarily for problems of severe joint instability and deformity not amenable to condylar replacement.

The condylar, non-constrained, tibiofemoral units are smaller and utilize a femoral stainless steel or cobalt chrome alloy mated with a polyethylene tibial component or components to replace the articulating joint surfaces. Gunston, who originated this approach to knee replacement, made a significant contribution by relying on ligamentous and capsular structures for stability. Fixation of the components is obtained with methyl methacrylate.

Wound healing, a prime requisite for successful knee-joint replacement with either the hinge or condylar unit, is more difficult to achieve than in the hip region because of the subcutaneous location of the joint.

The science of knee replacement is in its infancy. Progress is encouraging, and many patients are gratified by the early results. However, few of

the condylar replacements have been implanted for more than three years. Bryan and Peterson reported on a large series, but few results were available with follow-up of more than one year, and it is too early to predict long-term results.

HARLAN C. AMSTUTZ, MD

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Bryan RS, Peterson LF: The quest for the replacement knee. Orthop Clin No Amer 2:715-728, 1971

Inheritance of Idiopathic Scoliosis

FOR MANY YEARS, the increased familial incidence of idopathic scoliosis has been known to those treating the disease. The orthopedic literature is replete with articles describing similar curvatures in identical twins, but until recently no definitive studies had been carried out to establish this belief statistically.

Wynne-Davies reviewed the case record of 180 patients at the Edinburgh Clinic and concluded that the inheritance of idiopathic scoliosis showed aspects of dominant inheritance.

In order to establish the inheritance of scoliosis in greater detail than was possible by history and physical examination alone, Cowell performed radiographic studies of the members of 62 families. Ignoring all curvature of less than 10°, he concluded that the inheritance of idiopathic scoliosis was by a sex-linked dominant mechanism. The fact that the gene was carried through generations but was not demonstrated and that there was considerable variability in the manifestation of the disease suggested that the inheritance had variable expressivity with limited penetrance.

The important aspect of this study by Cowell is the recognition of the need for radiological examination of the spine of all siblings of a child with scoliosis. Non-operative methods of treatment of spinal curvature are dependent on early recognition and the institution of corrective measures before the development of a fixed deformity.

THEODORE R. WAUGH, MD

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Current Treatment of Myelodysplasia

MYELOMENINGOCELE is the most common of the medically significant lumbosacral spine defects characterized by failure of fusion of the midline structures. It is estimated that in every 1,000 live births, one infant will be born with a major developmental anomaly of the neural axis, often termed spinal dysraphism.

Mortality in untreated cases exceeds 80 percent in most reported series. In 1959, immediate closure of the midline defect was advocated in Sheffield, England. With widespread acceptance of this treatment, early mortality rates improved and it now appears that late morbidity statistics are also improved. Early closure of the defect tends to improve nursing care and parental acceptance, and it reduces the incidence of further neurologic deterioration in uncomplicated cases. Review of the combined experiences in numerous American centers has failed to support the original British claim that immediate closure results in a return of neurologic function. Various neurosurgical shunt procedures have proved beneficial in controlling hydrocephalus, which occurs in up to 85 percent of cases of spina bifida.

Coordinated multidisciplinary care involving a pediatrician, neurosurgeon, urologist and orthopedist affords not only maximum integrating of patient's care but invaluable inter-specialty exchange of therapeutic concepts in this difficult disorder. Regular urologic evaluation is increasingly important in view of the greater incidence of chronic renal disease with advancing age. With increased survival both the incidence and the severity of scoliosis of the spine are increasing. The combination of early fusion plus newer fusion techniques involving both the Dwyer and Harrington instrumentation has provided some promising early results.

Recent review of the past 12 years' experience in Sheffield has provided some tentative criteria concerning the ultimate prognosis of these patients. In cases with high level paralysis, hydrocephalus, spinal kyphosis or associated gross congenital anomalies, the ultimate prognosis is bleak in spite of years of massive coordinated medical care.

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Congenital Hip Dysplasia

THE PRESENCE of any sign of congenital dysplasia of the hip demands early treatment. The examiner must be aware that dislocation is rarely found at birth, but develops from dysplasia of the acetabular roof or laxity of the ligamentous structures holding the hip.

There is overwhelming evidence that the results of treatment directly relate to the age at diagnosis. The question becomes one of identifying infants with hips that can be subluxated or that have some evidence of instability, laxity, or dysplasia.

The most widely used test is the "clunk" of dislocation on examination of the hips of a relaxed infant at a time when he is not crying. Ortolani's name is associated with this test. The tight adductors on the side of an involved hip found with abduction testing of the hips is associated with Barlow's name. The asymmetry frequently found in the gluteal folds, leg length differences, or differences in positioning of the legs at rest should all alert the examiner of the likely diagnosis. Bilateral involvement becomes more difficult to diagnose and the need for x-ray studies combined with physical findings becomes more apparent.

As results are excellent with early diagnosis and splinting, it is mandatory that every infant be carefully examined for "loose hips." This is especially true in light of the relatively dismal comparative results of late diagnosis and treatment of congenital dislocation of the hip. The most highly suspect group is made up of children who were breech delivered or who have a family history of hip dislocation. Late dislocation—during the first two years of life—may also occur, and for that reason repeated examination for this condition during that period is important.

Where examination of all neonates for congenital hip disease is carried out by an enlightened medical staff, rarely are late surgical salvage procedures necessary.

MICHAEL SHLENS, MD

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Present Status of Anterior Interbody Fusion in Treatment of Disorders of the Lumbar Spine

A PERSISTENT and significant incidence of failure following treatment of herniated nucleus pulposus of the lumbar region with laminectomy or with laminectomy and posterior fusion has led to the search for alternative methods of treatment during the past two decades. The technique of anterior interbody fusion of the lumbar spine has been applied to this problem at several centers. Both transperitoneal and retroperitoneal approaches have been advocated for anterior interbody fusion. The early applications of the anterior or anterolateral approaches to the lumbar or thoracic spine were for the management of tuberculosis of the spine and were used principally in Africa and in Hong Kong. Since then, several series have been reported, giving results of anterior lumbar fusion for disc disorders.

The indications for the procedure have varied considerably and range from "All types of lumbar disc syndrome at all ages," to "Use for salvage procedures only after posterior or posterolateral attempts at fusion have failed." Just as indications for the operations are hard to define, so are the results of lower lumbar spine fusion difficult to evaluate. Nevertheless, high failure rates have become more obvious with the passage of time, with the anterior interbody fusion technique. Disappointing results in spondylolisthesis have been attributed to sacrifice of the stabilizing effect of the anterior part of the annulus fibrosis. For this reason, Hoover looked upon the use of the anterior approach for arthrodesis in spondylolisthesis as illogical. Furthermore, he expressed the opinion that owing to the vast differences in incidence of fusion, evaluation of the reliability of the procedure would be difficult. The report of Taylor on 226 cases treated by the Harmon technique echoes this conclusion. The fusion rate in this series was only 44 percent and no close correlation was observed between the presence or absence of fusion and patient response. In particular, it was pointed out that results of the procedure were uniformly poor in patients with compensation claims. In Taylor's opinion, as well as in the opinion of Stauffer and Coventry, the operation should be regarded as unreliable, useful primarily as a salvage procedure when previous operation has resulted in posterior instability, or

where the procedure is required for direct exposure of lesions such as tumors or granulomatous infections of the spine. There seems little reason to refute this judgment on the basis of the available evidence.

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Immediate Treatment of Spinal Cord Injuries

A PATIENT with a spinal cord injury that is clinically complete at 24 hours, as determined by accurate neurologic examination, will not have functional cord recovery. It is generally agreed that laminectomy is of little value and routine use of it has now been generally abandoned among paraplegists and at spinal injury centers.

Recent experimental evidence indicates that the neurologic damage may be due to edema within the constricting pia mater, which reduces venous return from the cord tissue. This decreases oxygen tension and the neurologic tissue suffers irreversible damage. Cooling of the cord with iced saline solution in the early post-injury phase has shown promise of being a method of avoiding the edema and the increased venous pressures. High doses of steroid administration and myelotomy also have shown some promise of decreasing the destruction of the neural tissue. Some investigators have found evidences of extremely high levels of nor-epinephrine locally in the damaged spinal cord tissue and have demonstrated the microscopic auto-destruction of the cord within four hours following injury. They have shown some ability to reverse this destructive tendency with monoamine inhibitors.

At the clinical level at present, however, there is no method of recovering lost neurologic function in the complete spinal cord injury. Early immediate care should be focused at realigning the spinal canal. Surgical treatment is indicated only for patients who have gross dislocations which cannot be reduced by closed methods. Whether to stabilize the spine surgically or treat it in traction until it heals by body repair mechanisms depends on the judgment of the physician who is responsible for the total treatment program of the patient. There is no evidence that surgical stabilization will increase neurologic return; however, a stable spine allows more rapid rehabilitation training and earlier discharge from the hospital.

Lest bladder infection develop, a Foley catheter should be inserted immediately and the urinary output monitored for 24 hours. At the end of that time the catheter should be withdrawn and the patient treated with intermittent catheterization. This has now been proved beyond doubt the best method by far for treating the "neurogenic bladder" to avoid over-distension and chronic infection.

E. Shannon Stauffer, MD

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Little League Elbow

COMPETITIVE ORGANIZED BASEBALL PROGRAMS for boys in the 8- to 15-year age group have introduced new clinical entities such as Little League shoulder and Little League elbow involving the throwing arms of young pitchers.

Throwing a baseball hard as required by pitchers entails an abnormal whip-like action of the arm which places an unusual traction strain on the shoulder and elbow joints. In growing youngsters this traction strain is transmitted to, or through, the ununited epiphyses.

Comparative roentgenograms of both elbows of 162 youngsters in the 9- to 14-year age group demonstrated the so-called Little League elbow to be primarily involvement of the medial epicondylar epiphysis, with fragmentation, separation and accelerated growth noted in all 80 pitchers in the study. Less common, but more serious, were changes in the form of traumatic osteochondrosis of the capitellum of the humerus, head of the radius, and proximal humeral epiphysis.

Since these changes are caused by repetitious trauma, treatment is primarily preventive—rule changes to limit the amount of throwing by pitchers, and encouraging youngsters to report elbow or shoulder pain immediately and to stop pitching. The symptoms subside rapidly with rest at this stage, and the youngster can then resume

playing at other positions but should not pitch again until the epiphyses close. Coaches and supervisors should be educated that elbow pain in youngsters is due to epiphysitis and they should not recommend treatment techniques commonly used for adult pitching arms.

JOEL E. ADAMS, MD

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Hand and Foot Problems in Drug Users

COMPLICATIONS with the injection of drugs into the extremities have increased epidemically. The magnitude of complication ranges from cellulitis to gas gangrene. The most serious complications in the extremities have occurred following inadvertent introduction of particulate matter into the arteries of the limbs. They vary according to the agent, amount, site of introduction, filler-substances, and delay in treatment.

Historically, intra-arterial injections of drugs have been a complication of drug administration for anesthesia or radiography. Now drug users who are "mainlining" sometimes inadvertently inject drugs into an artery and need emergency medical treatment.

The severity of disease is determined by vascular spasm, thrombosis, and ischemia. Tissue necrosis occurs as a consequence of intimal necrosis, vascular obstruction, and infection. Vascular involvement of the lower extremities is more commonly associated with amputation.

The syndrome of accidental arterial injections is one of immediate severe burning pain along the distribution of the vessel injected. The sensation is referred to as a "hand trip." The pain begins in the fingertips and extends proximally to the site of injection. The signs of ischemia are blanching of the tips of the digits, and the nailbeds soon appear cyanotic. A peripheral pulse may or may not be present.

The early inflammatory signs may progress rapidly to extensive swelling and discoloration of the limb. With treatment the symptoms may subside or progress to tissue necrosis and gangrene.

A high index of suspicion of drug abuse must be maintained. Treatment must be prompt. The most important aspect of treatment is heparinization to prevent thrombosis. The limb should be elevated slightly to improve venous drainage but not so much as to restrict arterial flow. The use of intra-arterial vasodilators, high molecular weight dextran, sympathetic blocking agents, and oxygen to increase the PO_2 of arterial blood has been advocated. There has been disagreement as to the efficacy of some of the above agents. The use of papaverine, topical anesthetic, and sympathectomy has not been universally effective.

Fasciotomy may limit the extent of ischemic muscle contracture. Amputation has been required in a large number of cases.

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Chymopapain Chemonucleolysis

CHYMOPAPAIN is the major proteolytic enzyme in papaya latex. It was first used for lysis of the nucleus pulposus of human discs in 1963. The pharmacologic action of chymopapain is on the non-collagenous protein interconnecting molecules of long-chain mucopolysaccharides causing dissolution of the bonds. The absence of effect on collagen assures that the annulus and the dural sac serve as effective barriers to indiscriminate digestion of other tissues. The enzyme has no direct effect on neural tissue, but inadvertent subarachnoid injection causes major hemorrhage and even death in experimental animals.

The indications are identical to those for classical laminectomy and discectomy. No effect would be expected in patients with spatial compromise due to causes other than disc degeneration or rupture.

Chemonucleolysis is performed under general anesthesia with bi-planar image intensifier control. The injection is made by the right lateral approach to avoid the subarachnoid space.

Several investigators have reported results similar to ours: 76.3 percent of our 422 patients had some degree of symptomatic improvement; in 32 percent results were rated excellent (pain-free and normally active for age).

The major complication has been anaphylac-

toid reaction in about one percent of patients and a delayed primary hypersensitivity reaction in another one percent. Other rare complications have been transient foot drop, temporary neuritic pain on the side of the injection, and disc space infection.

While this new technique is still an investigative procedure, results in over 3,000 cases nationwide attest its efficacy and safety.

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Arthroscopy of the Knee

NEW INTEREST in direct viewing of the interior of the knee joint with the use of the arthroscope has come with the development of an improved instrument and the publication recently of an impressive *Atlas of Arthroscopy* by the Japanese doctor, Masaki Watanabe.

Excellent visualization is possible of all structures of the knee, including the menisci, except the posterior cruciate ligament and popliteal area. By use of a "through the lens" camera, detailed colored photographs of pertinent pathologic changes can be obtained.

The procedure is indicated in diagnostic problems—for example those associated with poorly localized symptoms in the knee, previous operation, monarticular arthritis, osteochondritis desiccans, diagnostic biopsy, determining the best surgical approach, viewing the patello-femoral mechanism under actual physiologic conditions, and diagnosis and prognosis in litigation cases. It is also useful for research purposes.

Jackson found it useful in 88.5 percent of the cases he studied, and Casscells and others have had similar experiences.

The procedure requires a general or spinal anesthetic. It takes about a half hour and patients may walk the same day, usually experiencing some pain or discomfort for a day or two. A sterile technique is used and infection has been virtually non-existent.

Contraindications are few, but include pronounced stiffness of the knee or sepsis elsewhere.

Accuracy in diagnosis comes only with quite extensive experience and the procedure is not recommended for the occasional user.

MILO A. YOUEL, MD

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EDITORIAL

Delhi Belly, Hong Kong Dog, Casablanca Crud, Montezuma's Revenge, Turista

BY WHATEVER SYNONYM, travelers' diarrhea remains a taxing problem for the physician trying to give practical advice in advance of travel. Despite the renaissance of information emerging from recent studies of bacterial diarrheas,[1] little has come forth to advance our knowledge of the cause, treatment or prevention of travelers' diarrhea. These points are well reviewed by Dr. Barrett-Connor in this issue of CALIFORNIA MEDICINE.

Etiology. The relatively few bacteriologic and virologic studies conducted on travelers' diarrhea have shown that most cases are not due to viruses or to the commonly accepted enteropathogenic agents, including salmonellae, shigellae, the enteropathogenic serotypes of Escherichia coli, Entamoeba histolytica, and Giardia lamblia. Nevertheless, epidemiologic evidence strongly implicates an infectious process.

A most attractive hypothesis to explain travelers' diarrhea holds that the "normal" bacterial population of a person's intestinal tract changes during travel as a result of exposure to the "normal" intestinal bacterial population in a new environment.[2] In this process of change, so the hypothesis goes, for many persons diarrhea is an intermediate stage. The pathogenesis of such diarrhea may include the invasion by foreign coliforms of upper levels of the intestinal tract,[2,3] areas that are normally sterile or nearly so. A recent important finding was the isolation of "nonpathogenic," toxin-producing E. coli from sites in the jejunum, duodenum, and stomach of indigenes (not travelers) in India, who were experiencing acute episodes of diarrhea.[3]

Future studies of travelers' diarrhea should include serotyping of E. coli strains before departure, and during and after episodes of diarrhea. In addition, studies should attempt to isolate coliforms as well as anaerobes temporarily colonizing the upper intestinal tract. Basic to the latter work, however, is further clarification of the normal anaerobic intestinal flora.

Efforts to determine factors that predispose to diarrhea should be continued. Immunity may play a role. Reduction of intestinal motility by opiates has been reported in animal studies to enhance the pathogenicity of certain bacteria in the upper small intestine. Speculative but intriguing is whether the changing diet of travelers might yet be shown to contribute to the invasiveness of ordinarily nonpathogenic enterobacteria. In support of this notion, a recent report by Bullen et al[4] suggests that the iron-binding proteins of mother's milk play an important part in the resistance of breast-fed infants to E. coli infection as well as related physiologic conditions in the small intestine.

Therapy. Dr. Barrett-Connor's suggestion that allowing diarrhea to continue may serve a useful purpose by eliminating the infective organism or enterotoxin is provocative but needs further study. Meanwhile, patients should be provided symptomatic relief by such agents as compound of opium (paregoric) or diphenoxylate hydrochloride (Lomotil®). The comparative effectiveness of the two drugs is not established. Additional therapy includes rest, fluids, and an appropriate diet for diarrhea. If, however, diarrhea and prostration persist for longer than the usual one to three days, or if blood or mucus appears in the stools, or if temperature elevation is more than low grade for about a day, the patient should be advised to see a physician for diagnosis. Such symptoms often indicate salmonellosis, shigellosis or amebiasis.

Chemoprophylaxis. No drug can be recommended at present for the prophylaxis of either

travelers' diarrhea or for enteric bacterial or protozoal pathogens. The efficacy and safety of the drugs promoted for these purposes are in dispute or need additional confirmation. Promising perhaps in selected cases is the use of oral nonabsorbed sulfonamides or antibiotics (with full recognition, however, of their potential for adverse side effects). Travelers to areas with poor sanitation and hygiene still do best to eat only what is cooked or peeled, and to drink only boiled or bottled water.

Of immediate concern is the drug iodochlorhydroxyquin (Entero-Vioform®), often prescribed in advance of travel or available abroad without prescription. Studies of its effectiveness for travelers' diarrhea are not convincing. The recent fascinating-tragic report from Japan[5,6] of an association between the use of Entero-Vioform and the onset of a severe neurologic disease—subacute myelo-optic neuropathy (SMON)—in thousands of persons, has led the Food and Drug Administration in this country to recommend that the drug not be used for travelers' diarrhea. Although a causal relationship between the drug and the syndrome has not been established, the association is strong. A suggestive case of SMON was recently described[7] in a returning citizen following use of Entero-Vioform abroad. Since Entero-Vioform is a hydroxyquinoline, we should be alert to the possible occurrence of the SMON syndrome following therapeutic use of the chemically related drug diiodohydroxyquin (Diodoquin®), a major drug for the treatment of amebiasis. For this disease, it seems prudent to withdraw Entero-Vioform pending further studies, but to continue to use the equally effective Diodoquin.

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Controversial Ethical Issues in Medicine

THE ARTICLE, "Euthanasia—An Overview for Our Times," which is to be found elsewhere in this issue, marks the second in a new series, "Controversial Ethical Issues," in CALIFORNIA MEDICINE. As far as is known the Committee for Continuing Study of Evolving Trends in Society Affecting Life is the first of its kind to be established in any medical association. It has a difficult but an enormously important assignment. It is the primary instrument of organized medicine in California to explore the many new and complex ethical issues affecting life which are already confronting physicians, their patients and the families of patients and society as a whole. These issues are not likely to go quietly away. They are certainly not to be swept under the rug. Nor will they be easily resolved.

We live in a time of changing values, or at least in a time when traditional values are being questioned and reassessed. This, coupled with scientific progress in medicine and human biology which is likely to be nothing short of fantastic within the foreseeable future, and the certainty that the cost of applying this mushrooming knowledge and technology in practice will be equally fantastic, foreshadows the need for many new kinds of value decisions affecting human life and well-being. These decisions will generally be made by patients, their families, or in some way by society, but physicians and even the medical profession as a whole cannot but be involved in them.

It is appropriate that these emerging ethical issues be more openly discussed and it is appropriate that the medical profession be an important part of these discussions. It is not too soon to begin to get our thoughts in order, both as physicians and as a profession particularly concerned with human life and the quality of life.

—MSMW

Mesenteric Vascular Insufficiency

IN THIS ISSUE Doctors Stemmer and Connolly present a highly readable compendium of clinical observations concerning the various pathologic disturbances of visceral blood supply. It is a thoroughly researched document which chronicles the entry of medical and surgical thought into an area which was once the sole domain of the physiologist. Since they first became aware of the increase of mesenteric blood flow that accompanies the entrance of food into the intestine, physiologists have sought to clarify the mysteries that influence visceral blood supply. They appear to have identified a unique and extremely sensitive vascular system which has an autoregulatory mechanism with vasomotor responses unlike those in other vascular systems. Exaggerations of these responses can precipitate profound pathologic disturbances. Examples are the spotty intestinal gangrene caused by clinical shock when other organ systems retain viability, and the massive intestinal necrosis in Gram-negative sepsis, left heart failure, and other chronic low output syndromes. That these can occur in the absence of occlusive lesions in the mesenteric vessels suggests a breakdown of the normal humoral and neural mechanisms that preserve intestinal blood supply.

Two California surgeons, Dunphy and Mikkelson, must be credited with beginning the new era in the clinical management of chronic visceral ischemic syndromes caused by mesenteric arterial disease. Although the existence of these syndromes had long been suspected, Dunphy was the first to show that symptoms of chronic postprandial abdominal pain were often premonitory to the appearance of fatal intestinal gangrene. Mikkelson almost 20 years later was the first to demonstrate that relief of these symptoms could be provided by surgical removal of an obstruction in a mesenteric artery. The accuracy of arteriographic diagnosis and the refinement of surgical techniques that have now made possible the successful reconstruction of occluded or stenosed mesenteric arteries have created new questions in diagnosis and management. Why is one so rarely able to demonstrate functional changes in the intermittently ischemic gut? Are there other intestinal syndromes besides the one characterized by epigastric pain after eating? Is prophylactic operation indicated for the asymptomatic patient with multiple visceral occlusive lesions? Is "mesenteric steal" a real syndrome since for it to occur one must postulate an amendment to the accepted rules governing blood flow? Should both arteries be reopened in the symptomatic patient with lesions obstructing both the celiac and superior mesentary artery? If only one artery needs revascularization, which should it be? In the absence of major differences in collateral blood flow, why do some patients with median arcuate compression of the celiac artery have severe pain relievable by operation while others are completely symptom free? It is to be hoped that in the foreseeable future another medical progress report will supply answers to these questions.

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On the Responsibility and Authority of Physicians

THERE IS MUCH to suggest that the responsibility and authority of the physician and of the medical profession have been in an overall decline for a number of years. There is also much to suggest that the medicine and the medicine man of the time have always been an essential component of any society, and that in a society as focused on health and well-being as is ours, there must be unparalleled opportunities for physicians and the medical profession to assume many responsibilities and to take many new kinds of authoritative actions for the betterment of the public health. It would seem that these are times for imaginative leadership and action by medicine and certainly not for abrogating the responsibility and authority of physicians.

There can be no question that the responsibility and authority of physicians have lessened con-

siderably in many aspects of patient care. The physician of yesteryear seldom gave detailed explanations; he made decisions in what he believed to be the interest of his patient, and he gave "orders." He did not even feel called upon to disclose the nature of the drug he was prescribing. He assumed both full responsibility and full authority. Now the law states that there must be full disclosure of all possible side effects and complications of any drug or procedure to be prescribed, and then the patient, having been fully informed and fully understanding, is supposed to make the decision. In hospital practice the "responsible" physician has come to share decision-making authority, and to a lesser extent responsibility, with a wide variety of intraprofessional and interprofessional specialists. These include quality control committees, utilization committees, nurse clinicians, health team managers and others. And where formerly the costs incurred and payment were largely a matter of responsibility and authority between physician and patient, this has now become a matter of responsibility and authoritative intervention by "third parties," including government, who pay more and more of the bills for patient care. It is not intended to say that this is all bad, but there have clearly been important changes in the authority and responsibilities of physicians which have altered patient care.

The emphasis on health and well-being which has developed in this nation during the last decade provides physicians and the medical profession with many new opportunities to assume responsibility and to act authoritatively, the authority being derived from the profession's knowledge, experience and expertise with respect to human health and its disorders and derangements. No other profession is as authoritative as medicine for this. It hardly needs to be argued that physicians and the medical profession indeed have an obligation to bring their knowledge, experience and expertise in human health authoritatively to bear, not only in the care of patients, but upon the problems of health care for persons not ill, upon what is now being called community medicine, upon the health care of the human environment and even upon the genetic care of the human species. It appears that to fulfill professional responsibilities throughout this spectrum of health care, which incidentally must also include the health of the delivery system itself, individual physicians and the profession as a whole should prepare themselves to:

- Give professional opinions based upon expert knowledge with respect to human health and its disorders,
- Participate in decision-making throughout the whole spectrum of health care, bringing the above expert knowledge to bear,
- Perform professional procedures and services as problem solvers, managers, skilled technicians, teachers or advisors, or advocates.*

It is suggested that if the above essential functions can be successfully performed throughout the whole spectrum of health care, the medical profession and organized medicine will have found a means to fulfill their obligations to their patients and to society within the modern context of medical and health care. This will require a substantial reassessment of what physicians should be doing and of what organized medicine should be doing, and of what they should be taught during their professional lifetime of undergraduate, graduate and continuing medical education. One can only wonder whether such a reassessment will occur, and if not, what the future holds for this profession.

—MSMW

*The physician and his practice: 1980-2000—Sixth Progress Report of the Committee on the Role of Medicine in Society, California Medical Association. Calif Med 116:71-95, Apr 1972.

CASE REPORTS

Refer to: Kane RC, Newman AB: Diffuse skeletal and hepatic hemangiomatosis. Calif Med 118:41-44, Mar 1973

Diffuse Skeletal and Hepatic Hemangiomatosis

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DIFFUSE SKELETAL HEMANGIOMATOSIS, a rare vascular proliferation involving multiple bones, may spread to the viscera. The diagnosis of this disorder can be difficult, as the course of the disease is long and the symptoms and signs are not specific.

Report of a Case

A Mexican-American woman, born in 1904, had been in good health until 1960, when she began to have generalized pain in her bones, including most of the long bones, spine, shoulders and neck. She was told she had abnormal bones, but no specific diagnosis was made. Dull pain, mildly exacerbated by movement, persisted, but the patient continued her usual activities until 1971. At that time she was found to have generalized osteoblastic and osteolytic lesions of bone that were thought to be secondary to metastatic carcinoma. No further diagnosis was entertained and no therapy was offered.

Two months later, dull, persistent abdominal pain, anorexia and abdominal swelling began. Paracentesis revealed blood-tinged fluid; cytologic examination showed no cancer cells. Shortly thereafter, she experienced increasing exertional dyspnea, weight gain, edema of the ankles and worsening anorexia and abdominal pain. She had a large effusion of the right pleura, a large, firm epigastric mass continuous with an enlarged nodular liver, ascites, and round, bony excrescences of the skull, long bones and ribs. Biopsy of bone and liver showed normal parenchyma with increased capillary prolifieration.

Four months later she was referred to this institution for evaluation. The patient reported a weight loss of 12 kg in the preceding six months. The abdominal pain was so exacerbated by meals that she was able to eat only clear liquids in small amounts. She reported no fractures, calculi, jaundice, fever or melena, and she had no previous history of liver disease or consumption of alcohol. The past medical history was unremarkable, and the family history suggested no evidence of a similar disorder. Three siblings were alive and well.

On examination the patient was wasted and appeared chronically ill. She was afebrile. The blood pressure was 110/70 mm of mercury with no orthostatic decrease, and the pulse was 90 per minute and regular. Respirations were 22 per minute and shallow. On examination of the skull two separate bony nodules, 1 to 2 cm in diameter, were seen projecting from the underlying occipital calvarium. The fundi were normal and the skin had no angiomas or telangiectatic areas. Fusiform bony prominences, 1 to 3 cm in diameter, were palpable on several ribs, and two were present on the right tibia. All were nontender and without bruits. A large effusion was present in the right pleura. The left lung and the heart were normal. The breasts were atrophic. The liver extended 10 cm below the costal margin and was quite tender to palpation; a large left lobe presented as an epigastric mass with a systolic bruit. The spleen was not palpable.

The hemoglobin was 12.1 grams per 100 ml, hematocrit 38 percent and platelet count 355,000 per cu mm. Red blood cell indices were normal, erythrocyte sedimentation rate was 23 mm per hour (Westergren) and white blood cell count was 6700 per cu mm with a normal differential count.

Routine chemical blood tests, liver function tests and serum protein electrophoresis were within

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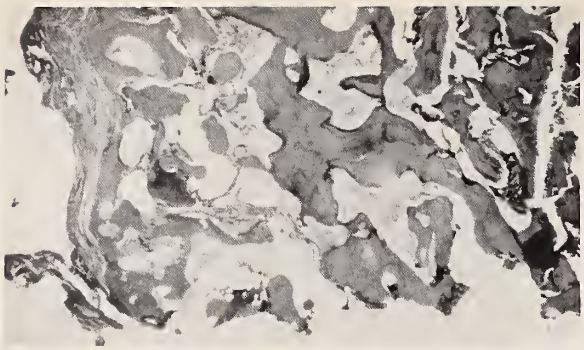


Figure 1.—Lytic area of the ileum. Cystic spaces of various sizes represent the angiomatous proliferation responsible for bony destruction (hematoxylin and eosin, × 10).

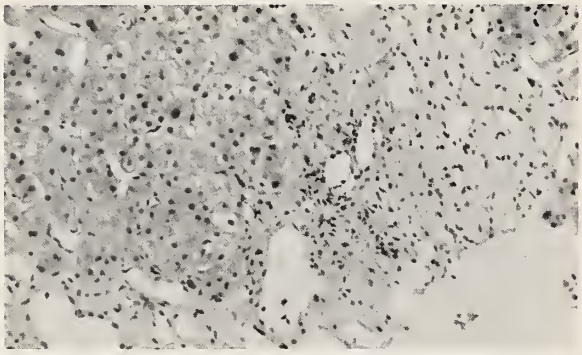


Figure 2.—Liver biopsy specimen. Cystic spaces on the right half of the specimen are lined by thin, homogeneously stained endothelial cells. Other areas of tumor contained numerous intraluminal red blood cells (hematoxylin and eosin, × 40).



Figure 3.—Hepatic arteriogram. Several lytic lesions and the fusiform, expanded area of the ninth rib are seen in this early phase of the hepatic arterial injection, which showed the diffuse vascular proliferation in the liver.

normal limits except for an albumin concentration of 3.3 grams per 100 ml. The serum alkaline phosphatase was 290 international units (three times normal), and by heat fractionation was of hepatic origin. Leucine aminopeptidase was also three times normal (90 international units).

Mammograms were normal. The pleural fluid appeared normal cytologically, with a protein level of 2.5 grams per 100 ml, and 200,000 red cells and 100 leukocytes per cu mm, with 90 percent mononuclear cells in the fluid. Blood volume and tagged red cell volume were slightly below normal. A liver scan showed an enlarged pattern with increased uptake in the left lobe and no defects of perfusion. An x-ray film of the chest showed the right pleural effusion and, in addition, osteoblastic and osteolytic bone lesions with several expansile, fusiform, densely sclerotic nodules in the ribs. A bone survey showed a similar pattern of bony destruction, without fractures, involving essentially the entire skeleton. The tissue sections of bone and liver (Figures 1 and 2) revealed numerous capillary angiomas and, with the bony lesions, suggested diffuse skeletal and hepatic hemangiomatosis.

Dyspnea from recurrent pleural effusion—despite chest tube drainage—limited the patient's ambulation. Continued loss of weight and abdominal pain led to further radiographic studies to define the extent of the patient's disorder and to determine if more effective therapy was feasible. An upper gastrointestinal series demonstrated extrinsic gastric displacement and esophageal varices. Transfemoral visceral angiogram (Figure 3) demonstrated normal major hepatic branches and innumerable diffuse capillary-sized hemangiomatous vessels (which accounted for the hepatic enlargement and bruit). There was rapid shunting to the hepatic veins and inferior vena cava and, in addition, retrograde filling of the portal vein, coronary vein, and gastric and mesenteric collateral veins. Hepatic arterial injection of epinephrine effected no significant change in the vascular pattern. The capillary hemangiomatous malformation causing the fusiform swelling of the right ninth rib was seen. The bowel and kidneys appeared normal. Venous pressure measurements and hepatic venography were done to evaluate further the hemodynamics of hepatic perfusion. There was some retrograde flow of contrast material from the hepatic vein through the liver, to the portal vein, and then into the gastric and esophageal varices. Midstream infrahepatic and suprahepatic

vena caval pressures were 2.0 cm of water and the wedged hepatic vein pressure was 38 cm of water.

Ligation of the hepatic artery to control hepatic hemangiomatosis[1] was impossible because the hepatic artery provided the only significant blood flow into the liver.

Narcotics were required for relief of abdominal pain; anorexia and dyspnea continued. In view of the effect that prednisone sometimes has on hemangiomas, especially those occurring in childhood,[2,3] a course of this drug, 40 mg a day in divided doses, was given. There was no symptomatic or clinical evidence of improvement; the patient died two weeks later.

The postmortem findings confirmed the diagnosis of diffuse skeletal and hepatic hemangiomatosis; no other primary or metastatic neoplasm was found. One of the rib lesions, which had expanded to involve the right pleura, and several subpleural angiomatous nodular proliferations, 0.1 to 0.4 cm in diameter, were the only apparent factors contributing to the pleural effusion.

Discussion

While the clinical course of the patient's final months was a malignant one, the histopathological appearance of the endothelial cells of the tumor (homogeneously stained, flattened and without mitotic figures) does not suggest angiosarcoma. In the 27 previously reported cases of diffuse skeletal hemangiomatosis,[4-7] the tumor was interpreted histologically as malignant in four.[4,6,7] The four patients had angiosarcomas, and death occurred within several months of clinical presentation.

A clinical classification of hemangiomas (Table 1) has been proposed[4] in which it is suggested that the number and location of tumor sites determine the mode of presentation. There is generally little transition between the major categories, yet within each there may be spread of tumor to contiguous sites.

TABLE 1.—*Clinical Classification of Hemangiomas**

Single hemangioma	Nonskeletal Skeletal
Multiple hemangiomas	Localized to one region Involving separate regions of the body
Diffuse hemangiomatosis ..	Nonskeletal Skeletal—with or without involvement of the viscera

*This table is a modification of the classification of Wallis et al.[4]

The single hemangioma is common, usually benign, indolent and found in up to 10 percent of all autopsies; histologically it is of two main types, capillary and cavernous; and the radiographic appearance is characteristic.[8] Syndromes associated with the single hemangioma include thrombocytopenia, disseminated intravascular coagulation and high-output cardiac states. This tumor usually appropriates for itself a blood supply from the circulation, with a major afferent and a major efferent connection. Those vessels in direct communication with the circulation contain red blood cells (and are the probable source of associated hemorrhagic effusions); the tumor vessels themselves often do not contain intraluminal red cells.

Multiple hemangiomas may or may not visibly involve the skin when confined to one extremity, may be similar in appearance to a single hemangioma or, rarely, may present as a syndrome of "disappearing bones"—that is, massive osteolysis, in which histologically benign hemangiomas completely erode bone and leave only fibrous tissue. Irradiation may arrest this process in some patients.[9] When separate sites are affected, the von Hippel-Lindau syndrome, the Sturge-Weber syndrome and other neurocutaneous disorders may be seen. Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)[10] is a form of diffuse nonskeletal hemangiomatosis; clinically evident capillary angiomas may not be manifest until adult life.

The long history and nonspecific clinical manifestations in the present case are typical of diffuse skeletal hemangiomatosis, the least common form of hemangioma. The greatest diagnostic problem in this disorder is the exclusion of metastatic carcinoma and plasma cell and lymphoid neoplasms. The abnormal vascular proliferation may be judged as incidental and noncontributory, or even overlooked in examination of biopsy specimens. Patients with carcinoma of the breast, stomach or prostate, as well as those with melanoma, carcinoid syndrome and Hodgkin's disease, may have mixed lytic and blastic bony lesions; bone expansion may occur with metastatic renal and thyroid carcinomas. How these neoplasms stimulate bone formation or destruction is unknown. The usual indolent course of diffuse hemangiomatosis may be interrupted by either of two occurrences: the development of angiosarcoma or the involvement of viscera. Death usu-

ally occurs within a year after invasion of pleura, lungs or liver becomes clinically apparent. The liver is the extraskeletal organ most frequently involved; pleural effusion, usually of unknown origin, is also seen. The extent of tumor outside the skeleton is considered the most significant factor influencing prognosis in patients without obvious sarcoma.[4] Extensive extraskeletal involvement, as in the case herein reported, represents a rapidly fatal malignant process.

The natural course of diffuse skeletal hemangiomatosis is poorly defined; it is usually progressive—lytic, sclerotic and expansile bony lesions increase with time, but not all progress concurrently. Angiomas probably originate in bone, but whether they are multicentric or metastatic in origin is unresolved. Some localized hemangiomas of bone have responded favorably to irradiation, and therapy with prednisone has been associated with regression of tumor. Alkylating agents have also been used, unsuccessfully, in childhood cases.[11] Occasional spontaneous regression in some patients makes evaluation of any means of therapy complex. There is no specific therapeutic intervention of demonstrated value at this time.

Summary

A patient with diffuse skeletal hemangiomatosis illustrates the natural history of this poorly understood disorder. The patient continued normal activities during a ten-year period of progressive involvement that ultimately affected her entire skeleton. There is no effective therapy for diffuse hemangiomatosis. Tumor invasion of viscera rapidly led to death in the case here reported.

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Refer to: Schrock TR, Dunphy JE: Malfunction of a colostomy in a patient with Crohn's disease. Calif Med 118:44-46, Mar 1973

Malfunction of a Colostomy in a Patient with Crohn's Disease

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CHRONIC MALFUNCTION of an intestinal stoma usually can be traced to a simple problem, such as stenosis, prolapse, hernia, subcutaneous fistula or an ill-fitting appliance. In patients with granulomatous enterocolitis, however, abnormal function of the stoma may result from the disease itself or from previous surgical intervention, or both. The case reported here illustrates the complexities that may be encountered in these patients.

Report of a Case

A 36-year-old Chinese woman was admitted to the University of California, San Francisco, Medical Center, on June 20, 1971, with complaint of liquid colostomy discharge for five years and cramping abdominal pain for two months.

She had had abdominal pain and diarrhea 15 years previously. The cause was diagnosed as "ulcerative colitis," and dietary measures were prescribed. Ten years later, a pararectal abscess was drained, a rectal stricture was discovered, and a sigmoid loop colostomy was constructed in the left lower quadrant. The sigmoid colon was described as thin-walled with no evidence of inflammatory bowel disease.

Two problems developed immediately after the sigmoid loop was divided to form a double-barrel colostomy: (1) stool egressed only from the inferior stoma instead of from the superior one as the patient and surgeon had expected; and (2) colostomy discharge was continuous.

Despite reassurances that all would be well in due course, for the next five years the patient was plagued by a bulky stoma which discharged 30 or more tiny liquid stools a day. A temporary appliance fitted poorly; because of leakage, the appliance was abandoned, and the patient relied entirely on masses of tissue paper to absorb the

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discharge. Exhaustive efforts to maintain hygiene were fruitless. Embarrassed by soilage, derided by her children for the prevailing fecal odor, and convinced that her condition was incurable, the patient became a recluse and did not venture from her home for three years. Eventually, cramping abdominal pain and weight loss over a two-month period prompted her visit to our clinic.

The patient was thin, distraught and appeared chronically ill. Digital clubbing was noted and a mass was felt in the right mid-abdomen. The bulky double-barrel stoma in the left lower quadrant was surrounded by hyperplastic granulation tissue and moist, erythematous skin. The superior stoma was a mucous fistula; the inferior stoma discharged green, liquid stool every few minutes. The rectum was stenosed five centimeters from the anal verge, and the perineum was scarred. Laboratory tests showed hypochromic anemia.

The colostomy was investigated radiographically (Figures 1 and 2). Radiographs after barium by mouth showed normal proximal small bowel. None of the radiographic examinations demonstrated the segment of colon from ileocecal valve to sigmoid, yet the medical records indicated that the colon had not been resected.

At laparotomy the conditions found were as shown in Figure 3. To correct them, the diseased small bowel and colon were resected, a permanent ileostomy was established, and the rectosigmoid was oversewn at the peritoneal reflection. The pathological specimen showed chronic granulomatous enterocolitis.

After an uncomplicated course, a permanent ileostomy appliance was fitted, and the patient was discharged on the eighth postoperative day. Her response was most gratifying. She was ecstatic and she quickly resumed social activities without fear of embarrassing herself or her family.

Discussion

Crohn's disease is notorious for causing abdominal fistulas. Many bizarre anatomical derangements have been reported,[1] but the combination of enterocavitary and sigmoidocavitary fistulas in a patient whose colon was excluded from the fecal stream by strategically located strictures is perhaps unique. The reversed sigmoid loop colostomy was an additional complicating feature in this patient.

A surgeon's responsibility to a patient with an intestinal stoma only begins with a technically excellent operative procedure; it includes educa-



Figure 1.—Barium study of superior stoma, demonstrating a sigmoid mucous fistula leading to a rectal stricture.

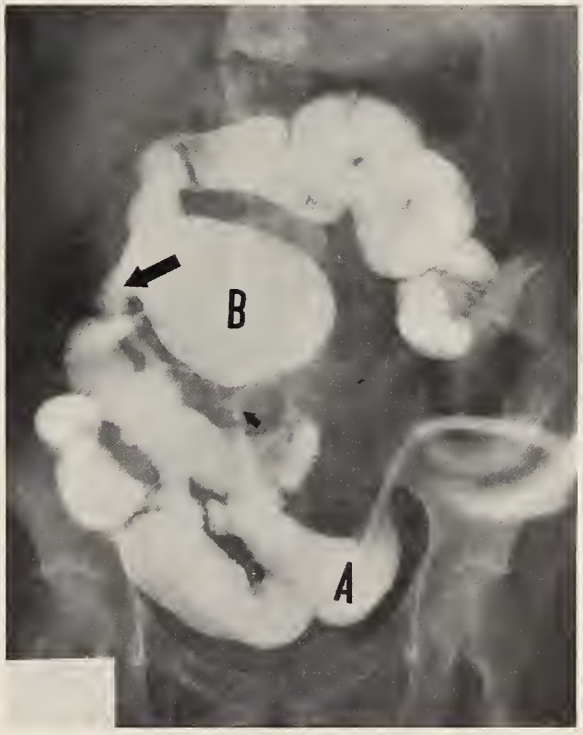


Figure 2.—Barium instilled into the inferior (functioning) stoma filled the sigmoid colon (A), passed through a tract (small arrow) into a saccular structure (B), then entered diseased distal small bowel through tract (large arrow).

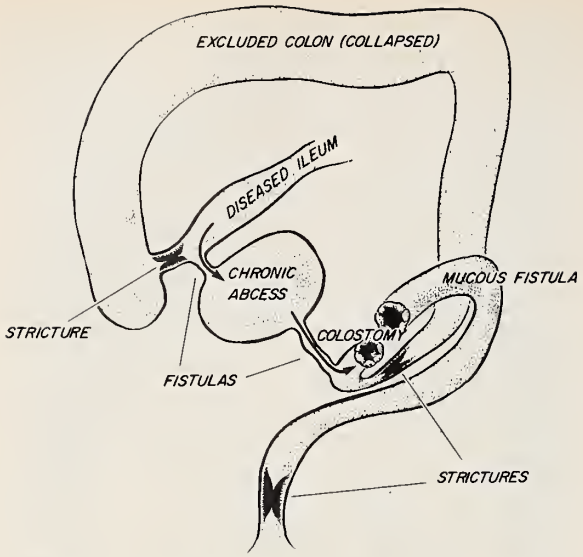


Figure 3.—The terminal ileum and colon were dramatically foreshortened and showed changes typical of chronic granulomatous enterocolitis. Structure (B) in Figure 2 was found to be a large chronic abscess cavity which filled by a fistula from diseased ileum and emptied via a fistula to the sigmoid loop which had been reversed during construction of the colostomy. Strictures explained the failure of the proximal colon to fill during radiographic examination.

tion and long-term rehabilitation. Malfunction of the stoma must be recognized, investigated and corrected if possible. A sigmoid colostomy should evacuate at regular intervals, once or twice a day; frequent discharge of liquid stool is clearly abnormal. Colostomy malfunction dating from the operation is usually due to inflammatory bowel disease, fistula, residual tumor or a serious technical flaw in the construction of the stoma. A patient who has profuse discharge from the stoma, difficulty with irrigation, or obstructive symptoms after initially good function should be examined for stenosis, prolapse, hernia, or recurrent disease.

The patient presented here was devastated both by her disease and its surgical management. Failure to recognize a problem and obtain an explanation caused severe distress over a protracted period.

Summary

A patient with Crohn's disease was incapacitated for five years by malfunction of a colostomy due to enterocavitary and sigmoidocavitary fistulas. She was rehabilitated by resection of diseased bowel and establishment of a permanent ileostomy.

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Cytomegalovirus Syndrome Post-Renal Transplantation

Treatment with Cytosine Arabinoside

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A CLINICAL SYNDROME occurring in four renal allograft recipients, consisting of prolonged fever, leukopenia and lymphocytosis which was attributed to cytomegalovirus (CMV) infection, was described in 1969 by Balakrishnan et al[1] and Andersen and Spencer.[2] The infection was documented by viremia and a rise in complement fixation (CF) antibody titer in the case reported by Balakrishnan et al and by viruria or a rise in the CF antibody titer in the three cases of Andersen and Spencer.[2] Remission occurred spontaneously in all four cases within one to two weeks of onset.

A similar clinical syndrome consisting of prolonged fever, leukopenia, lymphocytosis, hemolytic anemia and thrombocytopenia has been observed by us in nine childhood recipients of renal allografts.[3] Cytomegalovirus infection was documented by viremia, viruria or an increase in the CF antibody titer in each patient. This report describes the prompt remission of this clinical syndrome in a ten-year-old boy who had had an allograft, after treatment with cytosine arabinoside (Ara-C).

Report of a Case

The patient was a boy ten and a half years old who had been observed periodically at Children's Hospital of Los Angeles since age 15 months

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with a diagnosis of cystinosis confirmed by a slit lamp examination and bone marrow aspiration. Because of increasing symptoms of uremia, intermittent hemodialysis had been begun in April, 1971. He received a cadaveric allograft May 14, 1971. Tubular necrosis was severe and not until 19 days later was the allograft function sufficient to lower the blood urea nitrogen (BUN). A severe rejection episode occurred on day 21. It was resistant to increased immunosuppressive therapy and the allograft was removed on day 25. Intermittent hemodialysis was resumed and was continued until a second cadaveric renal transplant was carried out August 12, 1971. The allograft functioned immediately and postoperative dialysis was unnecessary. The clinical course of this patient after receiving the second allograft is shown in Chart 1.

On day 21 the patient began having daily temperature elevations to 40°C. The fever spikes occurred in the early morning and were accompanied by tachypnea, tachycardia and hypertension. Concomitant with the febrile episode were leukopenia (to a low of 1,400 per cu mm), rela-

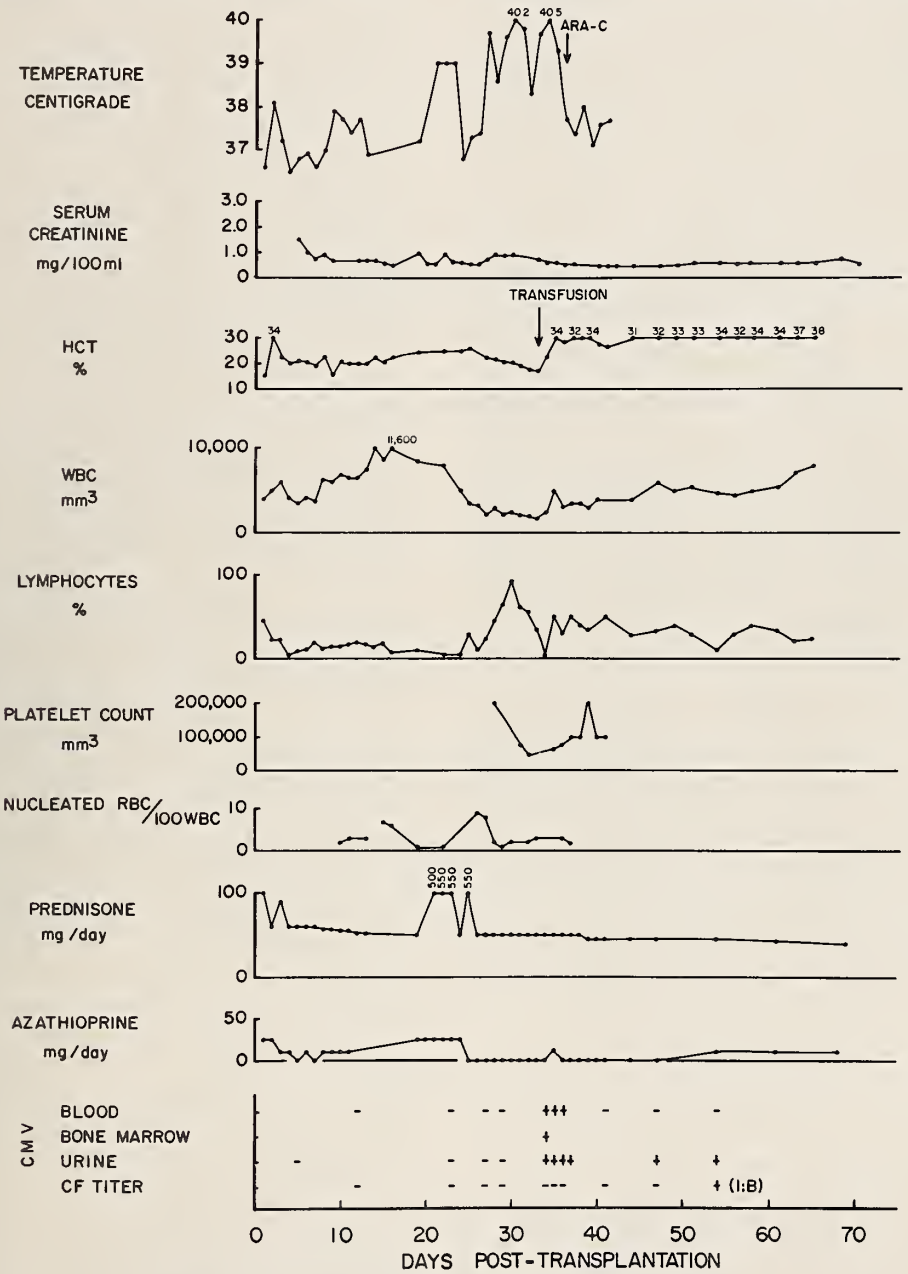


Chart 1.—Clinical course of patient in present case

tive lymphocytosis, thrombocytopenia (60,000 per cu mm), and anemia (the hemocrit fell to 18 percent before transfusion on day 33). Renal function as indicated by the serum creatinine level remained normal throughout the febrile period.

At first the fever was interpreted as a sign of rejection and the dosage of prednisone was increased (Chart 1). Azathioprine was discontinued on day 25 because of leukopenia and was not reinstituted until after remission of the febrile episode and elevation of the leukocyte count to more than 5,000 per cu mm on day 50.

The febrile period continued for 15 days and although the clinical and hematologic findings were consistent with CMV infection, neither cultural nor serologic confirmation was available during this period. The results of viral studies of the specimens submitted on day 34 became available only after clinical remission had occurred.

On day 35 it was decided that the persistence and severity of the clinical syndrome warranted a trial of Ara-C therapy. A rapid (5 minutes) intravenous infusion of 50 mg of Ara-C (3 mg per kg) was administered in the evening of day 35. On the following morning the characteristic early morning fever spike did not occur and two subsequent doses of Ara-C were given on days 36 and 37. The fever did not recur and the leukopenia, lymphocytosis and thrombocytopenia gradually remitted. No further clinical evidence of CMV infection has occurred and on the 82nd day after the allograft the serum creatinine was 0.6 mg per 100 ml.

Viral Studies

Collection of Specimens: A freshly-voided urine specimen (5 to 10 ml) or a specimen of blood (5 to 10 ml in a sterile, heparinized tube) were collected on the post-transplant days indicated in Chart 1. Bone marrow was collected on the 33rd post-transplant day. Ten milliliters of blood from each unit used for transfusion during the period of hemodialysis before the second transplant was collected and taken immediately to the Virus Research Laboratory for virus isolation and CF CMV antibody titer determinations.

Preparation of Specimens, Virus Isolation and Virus Identification: Specimens were prepared and viruses were isolated and identified as previously described.[4]

Serology: Plasma or serum was tested by a micro-complement-fixation test for antibody to human CMV antigen by the method of Sever et al.[5]

Results: Of six units of blood given to the patient before transplantation, two were found subsequently to have a CF titer of 1:8 or 1:16 for CMV. One of these units with a CF titer of 1:16 was administered 31 days before transplantation or 52 days before the onset of illness. This finding is suggestive evidence for the presence of latent CMV infection in blood donors, as previously reported.[6]

The results of the virus isolation studies from specimens of blood, urine and bone marrow before, during and after the febrile illness are shown in Chart 1. Cytomegalovirus was isolated from specimens of plasma buffy coat, urine and bone marrow on post-transplant day 34, 13 days after the onset of the clinical syndrome. Attempts failed to isolate CMV from specimens of plasma buffy coat or urine before or during the clinical illness on post-transplant days 5, 12, 23, 27 and 29. Although virus was isolated from the urine on three ooccasions after Ara-C was instituted (post-transplant days 37, 47 and 54), the virus was not isolated from the plasma buffy coat again. On post-transplant day 54 the patient's serum yielded a CF antibody titer of 1:8 for CMV.

Discussion

Histologic evidence of CMV infection has been frequently reported in postmortem examinations of renal allograft recipients.[2,7,8] The finding was usually fortuitous and not associated with clinical symptoms. Similarly, serologic evidence of CMV infection or cytomegaloviruria or both has been reported to occur frequently (22 percent to 73 percent)[2,4,8-10] in asymptomatic allograft recipients. The only reported clinical manifestations of CMV infection after renal transplantation have been the syndrome of prolonged fever and hematologic abnormalities[1,2] and the association of CMV with the transplant lung syndrome.[4,11]

The paucity of previous reports associating CMV infection with clinical manifestations in allograft recipients may be related to lack of persistent investigation. As shown in the present case, confirmation of CMV infections was not obtained until late in the clinical course. Previous descriptions have also indicated that the diagnosis of CMV infection usually is not made until after spontaneous remission of clinical symptoms.[1-3]

Although the causal role of CMV in the clinical manifestations of the present case cannot be unequivocally established, the association of CMV infection with the postperfusion syndrome[12] and heterophile-negative infectious mononucleosis,[13]

two entities that are manifested by prolonged fever and hematologic abnormalities, makes such a diagnosis likely.

Spontaneous remission usually occurs without significant morbidity in the above clinical syndromes ascribed to CMV; however, our experience has indicated the presence of significant morbidity in renal allograft recipients when the fever is prolonged—more than ten days—and when CMV infection is associated with transplant lung. Therefore, we decided upon a therapeutic trial of Ara-C when no spontaneous remission was evident after 15 days of illness.

Cytosine arabinoside is a pyrimidine nucleoside which inhibits deoxyribonucleic acid synthesis and has been shown to have potent antiviral activity *in vitro* against the human cytomegalovirus.[14] Recently, Ara-C has been used clinically to treat herpesvirus infections (varicella, zoster and simplex) both in previously healthy patients and in those with malignant disease. Dramatic clinical responses have been reported.[15] The response was usually rapid—within 24-72 hours—and the toxic side-effects were minimal. Because of these facts, Ara-C was selected for use in the present patient.

The response to Ara-C administration was dramatic. The fever spikes which had occurred daily for 15 days remitted immediately after the initial dose and did not recur. Likewise the hematologic abnormalities reverted to normal shortly after the initiation of Ara-C therapy.

Since the clinical syndrome which occurred in this patient has been observed to remit spontaneously in other patients, one may only speculate regarding the unequivocal therapeutic effect of Ara-C. However, the immediate response as manifested by the cessation of the febrile course seems significant.

The immediate response of the febrile course to Ara-C is possibly related to cessation of the viremia which could have been producing the fever. After the initiation of Ara-C therapy, CMV was no longer present in plasma buffy coat specimens. Conversely, cytomegaloviruria persisted for 16 days after Ara-C therapy. This may indicate that Ara-C is effective in eradicating viremia but possibly not in eliminating CMV from the kidney. Further trials in the use of Ara-C will be necessary to elucidate this point.

Summary

A ten-year-old boy recipient of a renal allograft acquired the cytomegalovirus syndrome, confirmed by virus isolations from his plasma buffy coat, urine and bone marrow, and a rise in the titer of cytomegalovirus complement-fixing antibody. Treatment with cytosine arabinoside after 15 days of clinical illness was followed by immediate cessation of the febrile course.

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LETTERS *to the Editor*

Drug Dosage for Allergic Rhinitis

To the Editor: The "Specialty Conference: Allergic Rhinitis" [Calif Med 117:37-44, Dec 1972], is excellent.

In removing Tables 4 and 5 for permanent use, I have checked the drug dosages of several of the drugs listed on Table 5 against the 1972 "P.D.R." and find the following discrepancies: Actifed® Syrup contains triprolidine hydrochloride 1.25 mg/5cc and not 25mg as stated in Table 5. The Actifed Tablet and Dimetapp® Elixir dosages are correct. Triaminic® Tablets (timed-release tablets) contain phenylpropanolamine hydrochloride 50mg, pheniramine maleate 25mg and pyrilamine maleate 25mg. Triaminic® Syrup is the antihistamine combination most commonly used in our practice because it can be obtained over-the-counter at low cost. This contains pyrilamine 6.25mg, phenylpropanolamine hydrochloride 12.5mg and pheniramine maleate 6.25mg/5cc.

The amounts of the drugs for the syrups shown on Table 5 are per 5 cc. This was not stated in the Table. I did not check the dosages on the drugs not mentioned above.

Talcott Bates, MD
Monterey

A Correction

To the Editor: Dr. Hamburger is on sabbatical leave; I am pleased to respond for the Pediatric Immunology and Allergy Division.

We are grateful to Dr. Bates for bringing the discrepancies in Table 5 of the Specialty Conference [Calif Med 117:37-44, Dec 1972] to our attention and very much regret that they were not detected prior to publication.

The table was intended to indicate some of the medications that are available and is by no means exhaustive; alternative formulations and dosages exist for many preparations.

The reference to Triaminic® is to the timed-release tablet which contains pyrilamine 25mg, pheniramine 25mg and phenylpropanolamine hydrochloride 50mg.

Dosages for all liquid preparations are for 5 ml.

H. Alice Orgel, MD, PH D
Assistant Professor of Pediatrics
Acting Director
Pediatric Immunology and
Allergy Division
University of California
San Diego, School of Medicine

Diarrhea in the Morning

To the Editor: I was interested in the extract from *Audio-Digest General Practice* titled: "Diarrhea in the Morning? It's Probably Functional" [Calif Med 117:74, Dec 1972].

In my experience I have learned there can be causes other than functional for morning diarrhea. I have been quite willing to rest on the diagnosis of a Functional Syndrome after first ruling out achlorhydria or even a severe hypochlorhydria.

I have had patients with morning diarrhea who had one of the thalassemias or chlorosis or Addisonian anemia (macrocytic-hypochromic) or carcinoma of the stomach.

Leslie Collins, MD
Sacramento

More on Abortion

To the Editor: In his article on "Mass-Produced Assembly-Line Abortion" [Calif Med 117:80-84, Nov 1972], Dr. Ford calls for scientific and rational facts demonstrating the value of legal abortion. In contrast, however, his highly charged and pejorative remarks reveal his own bias, but do not contribute to an objective understanding of the current status of abortion. With a casual quotation about the naturalness of pregnancy and an accompanying erroneous allusion to ecology, Dr. Ford dismisses the rights of women in a fashion shocking for a physician who purports to be concerned for their care.

In New York and California, where he decries the frequency of abortion, the availability of this procedure has dramatically reduced the maternal mortality formerly associated with illegal abortion. In addition, Dr. Ford referred to the Joint Program for the Study of Abortion, but failed to

note the significant fact that abortion mortality (8.2/100,000 abortions) was shown in this study to be significantly lower than maternal mortality in the United States (24.7/100,000 live births). Moreover, this liberalization of abortion has been temporarily related to a reduction in out-of-wedlock births after a generation of steady increase.

The recent decision of the Supreme Court of the State of California (The People vs. Robert W. Barksdale) found that abortion is a medical situation involving the doctor and patient and does not require approval by a hospital staff committee. The Court also noted that the language establishing medical criteria for approval of abortions was impermissibly vague. Furthermore, district attorneys and courts will no longer necessarily be involved with rape or incest cases. Termination in an accredited hospital by the 20th week of pregnancy remain standing as legal requirements.

Surely there is room for carefully reasoned differences of opinion in this controversial area of medical care which has grown so rapidly. Abortion services must be an accepted option in the medical care of women, and should be individualized rather than mass-produced. Each woman is entitled to make her decision with maximum self-knowledge and understanding. Polemic statements can arouse emotions, but gain little for those they purport to serve—the women of California who look to us for considerate, high-quality medical treatment.

ALAN J. MARGOLIS, MD
SADJA GOLDSMITH, MD
San Francisco

* * *

TO THE EDITOR: In the November, 1972, issue of CALIFORNIA MEDICINE appeared a long editorial by Dr. James H. Ford, titled "Mass-Produced, Assembly-Line Abortion—A Prime Example of Unethical, Unscientific Medicine." Although Dr. Ford quotes innumerable references, all very briefly, he uses very short quotations, sometimes out of context. This is certainly unscientific, and I would submit that it is probably unethical. Dr. Ford is obviously quite strongly on the anti-abortion side of this controversial issue. If one carried his logic out, nothing in medicine would be therapeutic, but all would be experimental. He is talking about guarantees of outcome which no one ethically can do in medicine. To be sure, the emotional impact of abortion on a woman of childbearing age is very great, and the follow-up evaluation of one's emotional status has not been studied in a scientific way with both controls and double-blind studies. This, however, has rarely been done in any psychiatric study and I suspect by current methodology is probably impossible.

But let's be blunt and face the issue. Most of the abortions that have been done for psychiatric reasons have been clearly not because the patient had been worked up well psychiatrically where extensive knowledge of her background was known to the psychiatric consultant, where there had been a generally long history of emotional upset. Indeed, I don't think anyone could seriously doubt that this has been a ploy in order to perform this procedure. It has, therefore, put the psychiatrist in a very uncomfortable position of making statements which are clearly not backed by adequate knowledge of his patient.

It is equally obvious that prevention, and therefore adequate contraceptive advice of whatever type would be preferable to abortion, and that abortion should be considered a back-up for contraceptive failure or lack of use. But it is also clear that to force a young woman to carry through a pregnancy that is unwanted has never in the past been demonstrated to be beneficial to her well-being and certainly an unwanted baby has several strikes against him when he enters the world. True, some have overcome this marked disadvantage, but lacking sufficient data and challenging Dr. Ford to produce some to the contrary, I would suspect that the large majority of children produced in this way end up with serious problems of not only psychiatric and social origin, but also of what we would consider strictly medical nature.

It seems to me that in discussing this issue the problem is one of the relationship of the patient and her physician and that the conscience of both have to be considered, and it probably has no more unethical aspects than the unnecessary tonsillectomy, hysterectomy or penicillin for a cold on the patient's request without adequate medical justification.

ROBERT L. BLACK, MD
Monterey

* * *

TO THE EDITOR: I read Dr. James H. Ford's article "Mass-Produced, Assembly-Line Abortion" [Calif. Med. 117:80-84, Nov 1972] with much interest and dismay. Interest, because he said very well a number of things that need saying; dismay,

because he did not so much as mention the major public health problems that underline the subject of his polemic.

These problems are two: First, in every country where abortions are *not* available legally under competent medical auspices, women obtain illegal abortions, either self-performed or through "abortion-mills." Supporting statistics include those from certain South American countries where the major cause of death of women of child-bearing age is abortion, even though the whole weight of government, the Church, and male-dominated custom prohibits abortions of any kind. Also, from the Encyclopaedia Britannica of 1959, "In spite of the legal hazard and maternal risk, induced abortion destroys about 16 percent of diagnosable pregnancies in the United States," about 1,000,000 per year! Conservatively this means at least 10,000 deaths and major complications per year, prior to the availability of legal abortions.

Second is the problem of unwanted children—with an estimated 50,000 abused and battered unwanted children per year in the United States.

There exists presently no really satisfactory answer to this problem. The solution not only cannot be as simplistic as suggested in Dr. Ford's article ". . . the medical profession should insist on such controls forthwith," but the adequate solution is not even foreseeable, at least to me. But surely the solution to these serious public health problems cannot result from considerations which completely ignore their existence.

BILL GAROUTTE, MD
San Francisco

Dr. Ford Replies

JUDGING FROM THE FACT that Margolis and Goldsmith have had to extend their attack to areas somewhat afield of my limited thesis: one must assume that my article, *per se*, is not easily refutable. In fact, in spite of a valiant effort to discredit me personally with *ad hominem* appeals, their opinions have actually failed to refute any of the specific assertions found in my synopsis. And this of itself would appear to recommend my article as worthy of some thoughtful consideration.

Now it would not be possible to adequately answer all the additional issues they have raised without writing another triple-length article (which I very much doubt the editor would abide). Take as just one example the irrelevant issue of women's rights. This is usually not injected into professional discussions about the ethics or indications for breast biopsies, C-sections, or other accepted, surgical interventions. Why then in this case?

In a similar vein, the recent California Supreme Court decision (I could write a book about this anomalous situation alone!) is also irrelevant to to the ethical issues dealt with in my article. Our profession has always recognized that the physician's conduct must be governed by a considerably higher ethical standard (*e.g.*, take fee-splitting or advertising by physicians) than the lowest-common-denominator type of behavior demanded by the state or the courts.

Admittedly, abortion is a "highly charged" subject—*no matter who discusses it!* Expressions about "polemic statements [arousing] emotions" would appear to be a case of the teapot calling the kettle black. As for such terms as "pejorative remarks," in this instance, I believe I am more sinned against than sinning.

And as for "bias," isn't everybody biased, for whatever reason, in favor of his own opinion? Then why is *my* bias singled out as something unique? The pretension that one has no prejudices is itself a very great prejudice. Aren't the abundant statements in my article by such liberal abortion advocates as Overstreet, Russell, Tietze, Sloane, Halleck, etc. indicative enough of my awareness of opposing opinion on this subject? When viewed in this light, can my article not be seen as demonstrating considerably more balance, and less bias, than many other articles on the subject?

Have Margolis and Goldsmith really studied my article and my references? Their gratuitous implication to the effect that abortion, as it is now being practiced in California, is "considerate, high-quality medical treatment" and a service to women completely begs the scientific question under discussion;—especially when such an implication is issued as an imperative to the medical profession at large. And using the "self-knowledge" of women as some sort of criterion for the the abortion decision only further obfuscates the matter. Furthermore, although they say they are against mass-produced abortion, apparently as a matter of principle; they also appear to be advocates of an abortion-on-request philosophy that has led inevitably to its establishment as a practical reality. Rather incongruous!

As for their statistics on abortion mortality: I must challenge that figure of 8.2 deaths per 100,000 legal abortions. Since these deaths are

under-reported to some unknown extent, this figure is based on rather soft data, and is not entirely credible. Please note that this latter allegation of mine is considerably more plausible than a similar implication made in recent years by liberal abortion advocates against the credibility of official U.S. government records, which have over the years shown only somewhat less than a few hundred deaths annually due to "illegal" abortions. (Instead, it has been asserted, quite implausibly, that there were actually 5,000 to 10,000 such deaths.)

In fact, almost all of these current abortion mortality studies are a virtual monopoly of liberal abortion enthusiasts. And their statistics are quite suspect and can readily be impeached;—if only on the basis of deficiencies in the collection of raw data. As Dr. Lester Hibbard, chairman of LACMA'S Maternal Mortality Committee, said (L.A. Times, 9-15-72): "There is under-reporting of therapeutic abortion deaths but to what extent nobody knows." Under these circumstances, Margolis' and Goldsmith's comparative analysis of "abortion" and "maternal" mortality rates can hardly be accepted, out of hand, as conclusive or elucidative of the total harmfulness of "legal" abortion.

Finally, Margolis and Goldsmith dismiss the statement of Eastman and Russell as to the naturalness of pregnancy too peremptorily. Will they assert, instead, that pregnancy is somehow unnatural? The fact remains that *induced* abortion is, by definition, an artificial (*i.e.*, unnatural) intervention into a natural physiologic process by the physician.

The question still remains: Is abortion really therapeutic in a given situation? Again, what are the objective criteria for making such a judgment? Of course, everyone is entitled to his own philosophical orientation, but those who would advocate any such surgical intervention should be prepared to document their rationale with scientific evidence that goes beyond superficial clinical impressions or mere philosophical preferences. In the absence of such evidence; the technique should be labeled experimental and limited to *small, well-controlled* studies, rather than be recommended for widespread, routine use.

Now, much of what I have said in answer to Margolis and Goldsmith is also applicable to the letters of Drs. Garoutte and Black.

My pro-abortion critics would have you believe that unless I incorporate statements compatible with *their* prejudices, my entire argument is thereby automatically invalidated. 'Taint necessarily so! I can assure them that the absence from my article of those many aspects of abortion which they seem so eager to debate is due to a lack of space, not to any lack of inclination on my part. I would be happy to do a series on every aspect of the subject, if Dr. Watts would permit. I have spent five years doing my research and am loaded with material!

It is ironic that the issue of bias should be raised so incessantly by pro-abortionists; especially in light of my two underlying reasons for writing this article; to wit: (1) to call attention to the virtual monopoly in the literature on this subject by pro-abortionists; and (2) to attempt to loosen the grip of this monopoly, ever so slightly, and to restore some balance to this extreme bias in the literature. I have scrupulously sought to reduce my own bias as a significant factor by using the findings and conclusions of eminent, liberal abortion advocates. If anything is to be refuted or repudiated, it must first and foremost be their own statements.

The charge that I have quoted "out of context" is unfair and untrue; as any interested reader can prove to himself merely by making his own personal review of my references. Throughout these references, liberal abortion advocates and experts are repeatedly demonstrating the gross bias, the contradiction and the lack of correlation and confirmability in data and conclusions. Some do this indirectly and inadvertently, but some honestly admit to these things, as well as to their own uncertainty, their lack of expertise, etc.

Regarding the use of statistics as evidence, I must again reiterate that many statistics put forth by pro-abortionists are easily challengeable as being unsubstantiated, highly selected, unverifiable, etc. "Please excuse my skepticism but I do not wish to deceive myself."

Dr. Garoutte oversimplifies my position, and then proceeds to call it "simplistic." I really did not offer any "solution." Rather, I have, in the best scientific tradition, merely delineated a problem (brought about by inadequate knowledge and excessive enthusiasm), and have called for further studies. (Incidentally, the extensive studies of Dr. Edward F. Lenoski of L.A. County-U.S.C. Medical Center indicate "that 90 percent of beaten children were planned pregnancies.")

Again, I feel sure that my critics here could not have actually read, thoroughly, all the articles

listed in my references. Otherwise, they could not have been so dogmatic about some of their statements. For example, Dr. Black challenges me to supply data to contradict his allegation that "the large majority" of unwanted pregnancies end up with serious social or psychiatric problems. But Forssman and Thuwe (Sweden) found that 48 percent of children from "unwanted" pregnancies were *completely free* of all the social and psychologic "defects" they were studying; which really compares not so unfavorably with 68 percent in the "wanted" pregnancy group. What this means then is that children of "unwanted" pregnancy had only 20 percent additional risk of social maladjustment above the posited norm, or above those from "wanted" pregancies. Hardly an overwhelming justification for having the former group of children destroyed without due process! Besides, the implication that it is better to be dead than maladjusted is hardly constructive or therapeutic.

And I can assure Dr. Black that if California physicians had done 116,000 tonsillectomies or hysterectomies in 1971 (95 percent for psychiatric or mental health reasons), I would be writing an article about the ethics of that also.

In conclusion, let me just point out that the very persistence of such disputes as these is perhaps the most obvious evidence available that more adequate studies of the abortion problem are badly needed.

JAMES H. FORD, MD
Lynwood

The Heart Surgeon

TO THE EDITOR: For reasons of their own, the news media, The American Heart Association and certain hospitals have given the concession of heart surgery to certain favored men, while excluding all other members of the specialty from working in that area.

When one surgeon is selected as "the heart surgeon" and given the monopoly in this branch of surgery, he is prone to develop the "God" complex; that is, he comes to believe and to assume that he possesses certain superior qualities which set him above his colleagues. He acquires a worshiping and adoring entourage who follow him unquestioningly and continually add to his problems by flattery. The favored one is denied the checks and balances by the free, independent, private practitioners in his field; this criticism, which acts as a governor, tends to keep us all in line. The surgical review committee would never dare to critically review the "Great One's" cases. While the Chief of Surgery would not hesitate to notify one of the excluded thoracic surgeons that he could not perform a procedure in his specialty, (since these procedures are reserved for the favored surgeon) he would not dare question any procedure scheduled by the "Favored Surgeon." The selected surgeon becomes overblown, overinflated, overconfident, resulting in incredible behavior on the part of these "superstars."

Those surgeons who have been excluded and denied the opportunity to participate in the newer developments in their specialty, tend to be forced in the opposite direction. To the degree that the selected surgeon is overinflated, the excluded ones become deflated both in their own eyes and in the eyes of their colleagues and the public. The excluded surgeons lose confidence and since they have been excluded also from the dog laboratory and excluded from clinical heart surgery, no matter how many post graduate courses they may take or how proficient and knowledgeable they may become in heart surgery, they still are not allowed to do it. It is contradictory to insist that people keep up in their specialty and at the same time to deny them the opportunity to do clinical work.

For the good of the profession, the Cult of Personality Worship ought to be discouraged by restoring full privileges to all surgeons in their speciality.

JOHN E. SUMMERS, MD
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Refer to: Euthanasia: An overview for our time—A report by the California Medical Association Committee for Continuing Study of Evolving Trends in Society Affecting Life (Controversial Ethical Issues). Calif Med 118:55-58, Mar 1973

Euthanasia—*An Overview for Our Time*

A Report by the CMA Committee for Continuing Study of Evolving Trends in Society Affecting Life

The Committee for the Continuing Study of Evolving Trends in Society Affecting Life was established by the CMA House of Delegates in 1971, following the consideration of a number of resolutions on the topic of abortion. The committee's charge was broadened, however, to include topics such as euthansia, biomedical engineering, medicine and religion, ecology and education. The committee's discussions, as its name indicates can cover a wide range of fields of interest to the medical profession. The following article is the first of several which the committee plans to publish, although the products of its deliberations may take the form of resolutions to future meetings of the House of Delegates.

The Committee on Evolving Trends in Society Affecting Life has been charged by the CMA House of Delegates to conduct a study of societal trends affecting the practice of medicine. A concomitant aspect of this study must be the anticipation of possible confrontations between present and future patterns of practice. Foremost is the present need to clarify certain terms which appear to be used interchangeably, thereby leading to confusion and misunderstanding, both within and outside the medical profession.

The technological advances of our generation are testing the nature of medicine and of historical medical traditions and definitions. These changes are creating an ambiguous situation in which, for example, "euthanasia" is equated with the abandonment of extraordinary means for maintaining life. Both the fallacy of the equation and the real questions of the application of "euthanasia" in medical pratice today can be clarified, perhaps, by an examination of the issues with which society is confronted.

Euthanasia has been defined as the *painless putting to death* (Webster's Seventh New Collegiate Dictionary) of persons suffering from incurable illnesses. It has also been described as "mercy-killing." For the purpose of this paper, however, mercy-killing will be defined as positive euthanasia—an intentional, positive act of interference with the natural history of the disease process resulting in the termination of the individual life. It should be noted that, at present, positive euthanasia is nowhere tolerated legally in the Western civilization.

The time-honored Judeo-Christian and medical ethic* has been to do all in one's power to preserve life.[1] In past times this meant solely allowing

This report was approved for publication by the Committee, November 8, 1972, and submitted for publication November 9, 1972.

Members of the Committee are: Samuel Horowitz, MD, Chairman; Walter Ellerbeck, MD, James H. Ford, MD, George K. Herzog, Jr., MD, Homer Peabody, MD, Dale W. Ritter, MD, Edgar Wayburn, MD, and Albert E. White, MD.

Reprint requests to: Committee for Continuing Study of Evolving Trends in Society Affecting Life, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

*In an address, "The Prolongation of Life" (1957), Pope Pius XII noted that it is incumbent on the physician to take all reasonable and extraordinary means of restoring the spontaneous vital functions and consciousness. "But normally one is held to use only ordinary means—according to circumstances of persons, places, times, and cultures—that is to say, means that do not involve any grave burden for oneself or another." It is the Church's view that a time comes when efforts should stop and death be unopposed.[2]

Also note the Hippocratic Oath, "I will give no deadly medicine to anyone if asked, nor suggest any such counsel."

the patient to die, since the state of the art provided no other course. The original concept of medical care was that of being primarily a nursing and comforting phenomenon. There was seldom any likelihood of actually curing the patient until recent times. The motivation was humane and individualistic. The physician's responsibility was to the patient; primacy for general social concerns over the patient's welfare arose only in times of threat to the community as a whole—as in natural disaster or war. Thus, the ethic of allowing a person to die was based entirely on consideration of the dying patient's state, not on the benefits that could accrue to others. While in former times no one would consider "allowing the patient to die" as an act of euthanasia, in light of today's changes one must call similar acts *negative* euthanasia, the termination of life through non-intervention in the disease process. Though the outcome of positive and negative euthanasia is the same, the intent is different. In the former the agent of death is some other person, in the latter it is the illness. The distinction is important and worth noting.

Time and technological progress have provided the physician with a life-prolonging armamentarium. It is thus that the conflict has arisen between the Judeo-Christian tradition and the sociological trend toward negative euthanasia—*a concept unknown but practiced years ago*. Prior to discussing the several theories already developed by protagonists of negative euthanasia, it will be helpful to examine the changing definition of the word, death. Medical literature is replete with examples of the difficulty of determining if death has occurred in some cases. From ancient times it was known that when the heart and respiration ceased, the brain would die in a few minutes. Now the traditional signs of life—heartbeat and respiration—can be maintained entirely by machine. Resuscitative and supportive machines restore "life" as judged by ancient standards, even when there is no possibility of the individual recovering consciousness following massive brain damage. Hence, the debate over the status of brain death. Some argue that the determination of brain death is a medical-scientific occurrence—that is, a matter of verifiable fact. Others hold that determining death is a socio-moral question—a matter of what is useful or good for the patient or society.† Is "pulling the plug" on the machine an act of recognition that death has occurred, or a halting of extraordinary means to continue life (negative euthanasia), or is it positive euthanasia? Under the circumstances, the historic definition and criteria of death are obsolete or, at least, need refining.

The most comprehensive criteria for brain death have been proposed by the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death.[1] The Ad Hoc Committee was concerned only with those comatose individuals who have no discernible central nervous system activity (but does not include patients with hypothermia—temperature below 90° F—or under the influence of central nervous system depressants, such as barbiturates) and who are, therefore, within the definition of somatic death. There is a difference between somatic death, which is death of the whole, and necrosis, which is death of a part within a living organism. Irreversible changes of certain vital tissues, particularly those of the central nervous system, cause the death of the organism as an integrated functional unit, and death of the individual.[3,3a,4] The Ad Hoc Committee's criteria are, in simplified form, (1) unreceptivity and unresponsivity to externally applied stimuli and inner need, (2) no movements or breathing, (3) no reflexes, and, when possible, (4) flat electroencephalogram. The tests are repeated at least 24 hours later with no change indicated in the foregoing results.

The Harvard Committee has recommended that, when the patient is hopelessly comatose, the family and all medical staff involved should be informed. "Death is to be declared and *then* the respirator turned off. The decision to do this and the responsibility for it are to be taken by the physician-in-charge, in consultation with one or more physicians who have been directly involved in the case. It is unsound and undesirable to force the family to make the decision."[1] It has further been recommended that, to avoid self-interest, physicians involved in the decision to declare the person dead not be involved in any later decision to transplant organs from the deceased patient.

If the Harvard criteria and procedural recommendations for brain death are accepted, then "pulling the plug" is not even negative euthanasia, but the recognition that death has occurred.

In the event that much controversy were engendered concerning new medical criteria for death, it might be necessary in various states to legislate the matter to avoid arbitrary or situa-

†In an address, "The Prolongation of Life" (1957), Pope Pius XII indicated that brain death is a medical problem, and that verification of the moment of death can be determined only by a physician. It is not "within the competence of the Church" to do this.[2]

tionist criteria. The courts traditionally have left medical definitions to physicians. *Black's Law Dictionary* states that death is "The cessation of life; the ceasing to exist; *defined by physicians* as a total stoppage of the circulation of the blood, and a cessation of the animal and vital functions consequent thereupon, such as respiration, pulsation, etc."[1] On May 26, 1972 (Tucker vs. Medical College of Virginia) a jury in Richmond, Virginia accepted the Medical College of Virginia's decision to declare a patient's death, using brain death criteria. The case has far-reaching implications for the medical profession.

Medical technology can significantly prolong the lives of the hopeleslly ill and the very old, who increasingly fill hospitals and nursing homes, drain facilities, personnel, and funds, and sometimes cause an acute scarcity of resources for other patients. It is asked by some if it is worthwhile to expend so many resources on terminal patients, or whether it would be better to promote euthanasia and/or allowing such a patient to die so that another patient *with more chance for recovery* can take his place. This is a utilitarian idea, and supplants the traditional humanitarian ethic of allowing a person to die, founded on concern for the individual patient's state, and not on benefits to others.

An analogous situation is the inequity between the scarcity of donors for transplant organs, and the growing number of patients in need of transplant organs for survival. Some such patients are old, have no dependents, or cannot work; others may be younger, have families, or have the potential to work: which patient should receive the transplant? Presuming that the patient wants to prolong his life, or is unable to express his wishes due to a condition such as paralysis or senility, critical decisions about the patient would be made without his consent.

The utilitarian framework for medical care debates the right of the individual against the public interest. One must consider who would be involved in the debate, how the public interest would be determined, and the ramifications of such involvement.

It is possible to approach the problem from a socio-economic standpoint, utilizing the cost-benefit analysis approach. "The life of the dying patient becomes steadily less complicated and less rewarding, and, as a result, less worth living or preserving. The pain and suffering involved in maintaining what is left are inexorably mounting, while the benefits enjoyed by the patient himself, or that he can in any way confer on those around him, are just as inexorably declining. As the costs mount higher and higher and the benefits become smaller and smaller, one may well begin to wonder what the point of it all is."[3] The moment when it would no longer be worthwhile to maintain a patient's life would be the point at which the rising cost and declining benefit curves intersect.

Inherent in such an equational approach to health care is the question whether health and life in some cases are an expensive privilege for the physically, socially fit, as determined by experts. Some fear that such subordination of medicine to social and economic needs rather than to individual, human ones compromises the medical profession's integrity and increases the possibility of having medicine subordinated to political needs as well. If there were to be political control, the category of expendable people could be extended from the sick to those deemed socially, politically, or racially undesirable.[5]

The patient's family may be involved in the life-or-death debate. Financial cares are often influential. If the family members have plentiful funds to prolong the patient's life, they may not hesitate to do so; if extending his life is a financial burden, they may wish otherwise. This situation raises the question whether health and life is a right or a purchasable commodity. The family may also be confused about medical aspects of the case, and thus not make an informed decision. Motivations such as feelings of guilt or malice can enter into the decision-making process, as well.

If physicians were to attempt to determine, on the basis of comparative medical evaluations, which patients had most chance for recovery and would therefore be treated, the result would be a shift in the orientation of the medical profession. Physicians would no longer serve the interests of the patient, but of society; physicians would not be providers of aid and comfort for the ill, but technicians of rehabilitation. Another problem which could arise is self-interest or conflict of interest.

Perhaps the most balanced, integrated approach possible for considering who would receive medical attention is the group decision. There is such a group in Seattle, which decides which patients will be accepted for dialysis treatment. The group is made up of physicians, a lawyer, a housewife, a businessman, a labor leader, and a minister. Thus, the community participates. The group

"considers two bases for selecting patients: the medical-psychological aspect and the social-moral, rehabilitation one . . . In choosing candidates, they consider 'worth to the community'."[6] For example, a thirty-two-year-old man with a family of six to support and a stable history of employment was chosen over a forty-five-year-old widow whose children were grown up and had left home.

With increasing technological power has come methods of prolonging life and treating illness which tend to impoverish the context in which people die. Fewer and fewer people die in the company of family, friends, or even medical personnel. "At that time of life when there is perhaps the greatest need for human warmth and comfort, the dying patient is kept company by cardiac-pacemakers and defibrillators, respirators, aspirators, oxygenators, catheters, and his intravenous drip. Ties to the community of men are replaced by attachments to a community of machines."[7] The situation has fostered the suggestion of a new right to *die with dignity,* a right which would have several components and which might entail euthanasia.

Protagonists of negative euthanasia as defined, state that death with dignity means that the patient must be told the truth about his condition if he wants to know it; he must be cognizant of his approaching death so that he can individualize it by making decisions. He may have arrangements, accounts, or promises to settle, religious ceremonies to perform, and loved ones to bid farewell. Another component of a death with dignity is human company and caring, they state. A third ingredient is to die unmolested by bothersome treatments, once they are judged useless in the particular case.

Does a death with dignity include the right to be mercifully killed? In some cases, such as protracted untreatable pain, the hastening of death may be thought necessary for a dignified death, and may be an extreme act of love. The idea of a death with dignity is solely beneficent for the patient; therefore, euthanasia would have to be considered only in terms of his interests. The patient, in sound mind, would have to spontaneously request such assistance, or have made previous, explicit arrangements concerning euthanasia.

In the eventuality that euthanasia were permitted under carefully scrutinized, supervised conditions, it would be difficult to establish a patient's *right* to be mercifully killed. Rights imply responsibilities, and if a patient had a right to be killed, a loved one or a physician would have the responsibility to kill him. While physicians have traditionally refused to kill, but have allowed patients to die when only extraordinary means would prolong life, it is not far removed from the humanitarian orientation of medicine, with the physician acting in the interests of the patient as a proxy, to hasten a terminal patient's death under special circumstances and when he requests it.

As can be seen, the morals, ethics, and dilemmas confronting the individual physician and the medical profession as a whole comprise a constellation of factors. Society as a whole will decide sometime in the future whether negative euthanasia will become accepted practice despite the protestations of segments within society. Without attempting to be judgmental, it is self-evident that the burden of the vital decision should not rest upon the individual physician. It is imperative that medicine maintain its role of healer, rather than executioner, if the public is to maintain its high degree of confidence in the profession. What must be decided, then, is who is to "bell this cat." It is suggested that hospitals consider formation of committees composed of administration, clergy, sociologists, and other community representatives of high repute, to whom the physician could address the facts of the individual case at the request of the family. If the committee decision is to "pull the plug," it is further suggested that the physician should withdraw from the case. Thus, society could best be served by having a decision made on its behalf implemented by a cross-section of its own composition.

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Telepede

A New Continuing Education Service for the Practitioner

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INTEREST IN FINDING NEW WAYS to assure a high quality of medical care for everyone is companion to current efforts to increase the quantity of care. How can the profession assist the harried practitioner to "keep up," burdened as he is with an increasing load of patients? Traditional methods of postgraduate education are often expensive of the practitioner's time, and frequently not directly related to everyday problems in patient care. Recently, the University of Southern California School of Medicine, Postgraduate Division, has shown that relevance and enhanced motivation for study can be gained by organizing study groups within the community hospital and providing them with materials and occasionally mediated consultations with faculty members from the medical school.[1] In this setting, the subject matter is selected by the practitioners, based on their needs, and the learning experience appears to be enhanced by group interaction.

Another, and even more directly problem-oriented educational apparatus, would be the provision of an antenna atop the ivory tower. This would receive incoming calls from the perplexed practitioner and would return instant wisdom. Some such device has been operational in Alabama, where the University of Alabama has instituted a Medical Information Via Telephone system (MIST) which is available to all physicians in that state.

In November, 1970, a telephone consultation service was made available to over 900 practicing physicians in Southern California to help them with difficult or urgent pediatric problems.[2] This service was initiated by Chapter II of the American Academy of Pediatrics with the cooperation of Children's Hospital of Los Angeles, whose staff provides the consultations. The feasibility of the service has been evaluated by the Postgraduate Division of the USC School of Medicine. Data accumulated during the first three months of operations form the basis of this report. Information was sought on several aspects:

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1. Will the service be used?
2. Does the calling physician find the service useful to him?
3. Is there any evidence that patient care is modified as a result of this consultation?

Use of the Service

In this pilot study, the service was offered to all 393 members of the American Academy of Pediatrics, Chapter II (eight southern California counties), and a similar number of members (444) of the American Academy of General Practice, plus the medical staff (116) of an urban community hospital. Of these 953 physicians, 574 indicated an interest in participating and during the initial three months of the feasibility study there were 108 calls from 82 physicians. These calls were received by trained nurse-operators who were able to direct them to an appropriate full-time member of the Children's Hospital staff (or, at night, a chief resident). During the first three months, 21 members of the Children's Hospital staff participated and since then most of the full-time staff physicians have answered calls. All members of the Children's Hospital staff (70 in all) have made themselves available for this service, at no cost to the calling physician.

The rate of incoming calls increased somewhat during this initial period; and since the initial three months of feasibility study the rate has remained at 20 to 30 calls a month, even though there was no publicity for the service after the initial announcement. This utilization parallels the experience of the MIST program of the University of Alabama. Fifty-five percent of all calls were from pediatricians and 45 percent were from general practitioners and other specialists practicing in a community hospital. The data indicate that a telephone consultation service will be used and provides a resource to both specialist and the family practitioner.

The kinds of problems presented dealt with all aspects of pediatric diagnosis and management, and required consultants in a wide range of pediatric specialties.[3]

Usefulness to Practitioner and Patient

Physicians who had called in were asked if the service had been helpful. Ninety-one percent replied that they were helped by the consultation, although only 36 percent felt that management of the problem had been altered as a result. This suggests that in the majority of instances the consultation served as authoritative reassurance to the practitioner, and that in about one-third of instances some change in diagnosis or management resulted. Thirty-six percent of the consultant group believed that the advice that had been given probably affected the prognosis.

Efficiency of the operation of the service was facilitated by using nurse-operators who determined the nature of the problem from the calling physician, selected the appropriate specialist, and arranged for connection through the hospital switchboard. Direct communication with the consultant occurred within five minutes 38 percent of the time and within one hour in 86 percent. In most instances (87 percent) the practitioner felt that the selected consultant was appropriate for his problem. No unusual medicolegal risks were anticipated from use of consultation service of this kind and no such problems are known to have occurred.

Of those who used the service, 94 percent said it should be continued. This expression and the already mentioned other indications of usefulness suggest that the scope of the service should be expanded. The consultants at Children's Hospital have expressed a willingness to continue their participation and have indicated that they would like to see other pediatric centers in southern California take part. Plans are being made to expand the service.

There are strong indications that a telephone consultation service may have considerable influence on patient care. As an educational instrument, it has the virtue of providing information and expert opinion that is directly related to the problems being faced by practicing physicians. And the communication is two-way: the consultant learns what kinds of problems the practitioner needs help with—information that can be used in the planning of more formal continuing education programs. The effect of such a consultation service thus extends beyond the individual user to the medical community at large.

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Health Services in Saskatchewan

North America's First Comprehensive Government-Sponsored Health Plan

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American People are becoming increasingly disenchanted with their present system of health care. As costs have risen, services for many citizens have become progressively less available. Changes of major significance seem imminent and inevitable. The question currently being asked is not whether we shall have national health insurance in America; rather, it is what kind of national health insurance will we have.[1] There is growing national consensus that a system of health insurance covering not just old people or poor people but all people is needed. Various proposals which would transform the health care system are being considered currently by Congressional bodies.

Introduction of a system of comprehensive health insurance is hardly a new idea; indeed, most countries of the western world have already devised and implemented such arrangements. But in North America it was not until 1962 that the first comprehensive government-sponsored medical insurance program was instituted. This event occurred in Saskatchewan, Canada. In 1970, as representatives of the American Society of Internal Medicine, Richard Burg and I visited Saskatchewan to study its health care system and to learn how the people there regarded the program. Of the peoples of the world, Canadians are most like us. We share many cultural heritages and we have a common language, similar systems of government and an interdependent economy. Experience in Saskatchewan may provide information of value in predicting how comprehensive health insurance might be received in this country: Can we learn from their experience, capitalize upon their successes and avoid their mistakes?

Historical Perspectives

The Province of Saskatchewan is almost as large as Texas but has a population of only one million. Grain farming is the main industry. The climate is extreme and rigorous in both the meteorological and the political sense. The people of Saskatchewan remember very clearly the Great Depression of the 1930's. In 1937 two-thirds of the population were on relief and many people

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lived on the very edge of life. The crisis and suffering of these times demonstrated the collapse of an old economic order; as a child of deprivation, the Cooperative Commonwealth Federation (CCF), a new socialist political party, was born. The party, now called the New Democratic Party of Canada (NDP), is more Christian than Marxist in its ideology; it rallied together trade unionists, socialists, intellectuals and supporters of the Farmers Progressive Movement.[2]

For some years before 1962, many cooperative medical programs existed in Saskatchewan; some examples are the Hospital Services Plan, Workmen's Compensation Program, Mental Health Program, Cancer Clinics, and Air Ambulance Services. Among the territories of North America, Saskatchewan in 1962 was unusually advanced in its social consciousness; government was already involved in providing health services.

In April, 1959, Thomas C. Douglas, the CCF premier, announced the government's intention to introduce a comprehensive medical care insurance plan to cover the entire population of Saskatchewan. Through this program, all residents of the province would be eligible to receive medical services. It was emphasized that medical services would be of high quality. The program would be under the sponsorship of the provincial government and be administered by a commission responsible to the legislature and, through it, the entire populace. The services would be acceptable to those providing and to those receiving them. Services would be paid for with contributory premiums forming a part of the revenue. Other funds would be received from a sales tax and from federal sources. Payment for physician services generally would be on a fee for services basis.

In 1960, a bitterly contested provincial election was fought around the issue of government-financed comprehensive medical care, and the CCF government was re-elected. As the government prepared its plan to introduce the Medical Care Insurance Act, the physicians there generally prepared to oppose it. The government proceeded rapidly to introduce the act, with little or no consultation with the medical profession in spite of previous promises that this would be done. The government commission was given power which extended far beyond an insurance plan and gave the physicians neither rights nor privileges, no bargaining rights to negotiate fees and no privilege of advising the government in any way unless the commission agreed.[3] On the other hand, the physicians gave the Medical Care Act the most perverse interpretation conceivable.[4] They aligned themselves with right wing political groups which associated their cause with cherished values; in so doing, they cultivated bigotry and prejudice.[5] The physicians rejected the decision of the elected representatives of the people of Saskatchewan and failed to appreciate the constitutional rights and obligations of a minority group in a democratic society.[4]

Each side rejected the proposals of the other. The Medical Care Insurance Act became law on July 1, 1962, and on that date the physicians of Saskatchewan withdrew their services.

Public opinion became severely polarized. Rallies and marches attracting several thousand people were held for and against both sides. Tempers rose and fists flew during these weeks of a long hot summer. Extremists from both sides participated in violent and destructive behavior. Wheels inexplicably came off automobiles, physicians' cars were forced off the road, walls were daubed with paint and caustic substances were poured on lawns.

On July 23, 1962, after intensive negotiations mediated by Lord Stephen Taylor, the College of Physicians and Surgeons and the government agreed to what came to be called the Saskatoon Agreement. The government agreed to withdraw the controls over conditions of practice contained in the original legislation and indicated that it was not its intention to establish alternatives to fee for service as the method of remuneration to physicians. The government also agreed that nonprofit insurance agencies would be preserved, though in modified form. Such was the stormy birth of the first comprehensive government-sponsored health insurance program in North America. In Canada, it is said that in the field of health care "what Saskatchewan does today, the rest of Canada will do tomorow." Since 1962, government-sponsored health insurance systems covering hospitals and physicians services have been extended to virtually the entire population of Canada.

The Plan

The Medical Care Insurance Plan provides insurance coverage to Saskatchewan residents for almost all services by physicians, plus refractions by optometrists; chiropractic services will be covered in the near future. There is no limitation of

benefits. The plan is administered by a commission. With other programs such as the Hospital Services Plan, Psychiatric Services and the Cancer Commission, it forms part of Saskatchewan's health services.

A health insurance premium is levied annually and collected jointly with the hospitalization tax. The annual premiums are $72 per family, of which $24 is for the medical and $48 for the hospitalization plan. The premium is waived for patients in financial need. The federal government contributes 65 percent of the costs of insured medical services provided; the balance is derived from the general revenues of the province. All beneficiaries under the plan receive the same coverage regardless of age or state of health.

In 1971 insurance payments for medical services were $34,310,000; this amount was up by 12.2 percent from 1970. The costs of the Hospital Services Program in 1971 was $90,517,400, an increase of 12 percent from the previous year. In 1963, the first complete year of operation of the medical care plan, the cost was $18,330,000; the cost of the hospitalization plan in 1963 was $43,706,000. The per capita utilization of medical services increased by 5 percent between 1970 and 1971, compared with a 3.6 percent average annual rate of increase between 1963 and 1971. Administrative costs of the medical care program in 1971 were 4.1 percent.[6]

The Medical Care Insurance Plan is administered by a commission consisting of not less than seven nor more than eleven members responsible to the Minister of Public Health. Three members are nominated by the College of Physicians and Surgeons of Saskatchewan. At present there are ten members, of which four are physicians; a physician is chairman.

How Physicians Are Paid

A physician receives payment in several ways. He may elect to submit a bill directly to the Government Insurance Commission and receive payment directly. Alternatively, if the patient is a member of one of the plans offered by the private nonprofit insurance agencies, the physician may bill the agency. The private agency then forwards the claim to the Insurance Commission, which recompenses the agency, and the agency then pays the physician. This arrangement was devised so that the physicians might choose to avoid having to negotiate directly with the government over money matters. In 1962, physicians wished to avoid being paid directly by government because of the potential damage which might be caused to the doctor-patient relationship. A third method of billing involves the physician's sending the bill to the patient. The patient then negotiates with the government and the government sends the patient a check; the patient then pays the physician.

The existence of these alternative methods of billing was a concession made by the government to the physicians at the time of the Saskatoon Agreement. In 1962, direct billing to the Government Insurance Commission was regarded by the profession as undesirable. Since 1962, however, there has been progressive acceptance of direct billing by the profession. Approximately 60 percent of all accounts are now sent directly to the Insurance Commission. The method of payment through private insurance agencies is a highly artificial system which reduces the function of these agencies to little more than that of a post-office service. Billing the patient and having him secure reimbursement from the government was advocated initially by some of the strongest opponents of the government plan; but it was discovered that patients might receive and spend the check and then indicate that they were unable to pay the bill. Billing the patient directly is not popular with the physicians.

The Medical Care Plan receives more than 65,000 claims each week for physicians, private health agencies, optometrists and patients. Information from the claim is transferred to key-punched cards which are scanned by a computer where the claim is subjected to a series of tests which determine if the account can be approved for immediate payment. The proportion of claims that fail to pass the tests is small; among the chief reasons for failure are that the patient's name, age or sex does not correspond with his health insurance number. One percent of accounts are duplicates and have been submitted and paid previously.

The College of Physicians and Surgeons and the government negotiate schedules of payment for physician services. In this bargaining process the strength lies with the government because it has ultimate fiscal responsibility. Bills rendered by the physician for payment by the commission must itemize the services given. As a consequence, an extraordinary wealth of information is available about particular services that the various types of physicians provide to the public.

Incomes of physicians have increased. Special-

ists are paid at the specialty rate if the patient is referred by another physician; he is paid as a generalist when he sees patients who are not referred.

The number of registered physicians in Saskatchewan has increased from 633 in 1950 to 895 in 1960 and 1,019 in 1970. There has been a progressive decline in the number of new registrants from Canadian medical schools and an increasing registration of foreign physicians. Saskatchewan has reciprocity with the General Medical Council of Great Britain. At present, approximately one-half of the new registrants are graduates of British medical schools.

Review of Professional Services

In 1964 at the request of the Insurance Commission, a Professional Review Committee (PRC) was appointed by the College of Physicians and Surgeons to study and analyze cost-related data. There are seven members; all are physicians. Various factors in each physician's practice (a "profile") are assembled quarterly and provide information about the amount and cost of services he provides. Analysis of the quality of care cannot be made from the "profile."

The medical branch of the Insurance Commission devises and formulates most of the studies which are referred to the PRC. Examination of the profiles reveals great variation in the services provided; some physicians, for example, order many electrocardiograms while others practicing in apparently similar circumstances order only a few. When a physician deviates by more than two standard deviations from the mean of others in the same category, his profile is referred to the PRC. In some instances there are obvious and legitimate reasons for the deviation—the physician may have a small referral practice and sees patients with complicated problems which require extensive and costly investigation. In other instances, reasons for deviation may not be apparent. The PRC may interview physicians and invite them to expain why their costs of patient care are significantly different from those of their peers. In instances where physicians seemed to be involved in providing an unjustifiable number of particular service items, the College has approved payment to these physicians at a reduced rate for these items.

A second kind of study examines the cost of a particular service; for example, nearly all bills for appendectomy indicated that "complications" had occurred. When medical records were examined, existence of complications could not be confirmed. The original payment schedule listed "appendectomy" and "complicated appendectomy" and assigned a higher fee for the latter. The schedule was subsequently revised to list only "appendectomy" (with or without complications).

The PRC has maintained a fluctuating level of activity; its energies have been directed toward investigating cost factors. There has been no significant study of the quality of medical care. The PRC reports and make recommendations to the College of Physicians and Surgeons. The College has varied in its responsiveness, but since 1970 it has supported the PRC more actively.

Attitudes Toward the Program

We asked many members of the general public if they would choose to return to the former ways of providing medical care insurance. The question was usually regarded as being ridiculous; "Of course not," was the usual reply. We asked people how much the health plan insurance cost them. Many seemed surprised at the question; others gave as their answer the amount of the annual premium. Few individuals had any idea of how much the program was costing them. The relationship of the sales tax to the health care scheme was usually forgotten, as was the federal contribution, derived to a large extent from federal income taxes.

Nurses and laboratory technicians were questioned. All agreed that the medical care program was popular with the general public. They expressed the opinion that the only opposition to the program lies with older physicians. Interviews with three social workers were of particular interest. They insisted that medical services were just as available to persons in economically deprived circumstances as to anyone else.

Several physicians were interviewed. Among older physicians and especially those who were directly involved in the dispute of 1962, resentment and bitterness lingers. They voiced suspicion that the Insurance Commission planned to extend their control over the practice of medicine, abolish fee for service remuneration and even direct physicians to practice in particular geographic areas of the province. Many young physicians, however, regarded the health insurance commission as a non-controversial part of their way of life.

Several members of the Department of Public Health of Saskatchewan were interviewed. All saw

an urgent need to control the rising costs of providing health care and were concerned that the general public had been "educated" to expect so much from the health care system. Only 3 percent of the budget is spent on preventive health and health education. We inquired about the concern which physicians expressed regarding government interference with their practices and their inability to influence when or how the rules which govern these activities might change. Representatives of the government indicated that it was very unlikely that the government would move in a unilateral manner which would adversely affect a profession whose practitioners are in short supply.

There can be no doubt of the popularity of the medical care insurance plan in Saskatchewan; the public strongly supports it and there is no significant opposition to it. If there was any major feeling against the program, at least one of the political parties would have adopted as part of their platform a resolution to restrict or rescind the program. All major political parties in Saskatchewan have endorsed the program and since 1962 every provincial government in Canada has adopted a program of health insurance. The federal government has encouraged these activities by providing funds to share the costs of such programs.

Discussion

The major problems facing the Saskatchewan plan are over-utilization of services by the patient, over-servicing by the physician, and escalating costs. In an effort to curb over-utilization, the Liberal government in 1968 introduced "utilization" or "deterrent" fees. The amount of the fee paid by the patient was $1.50 per office visit and $2.00 per home visit. A fee of this size does not represent a major deterrent except to those in economically deprived circumstances; the fees were abandoned in 1971.

Over-utilization is difficult to define in practical terms. If the utilization of preventive health service could be increased, the need for conventional services might be reduced. The development of a truly healthy society requires that social, cultural and educational barriers be surmounted. The ultimate target is a service oriented to health as well as to disease; the Saskatchewan program remains conventionally directed to disease.

Over-servicing by physicians continues to be scrutinized by the Professional Review Committee of the College. In Saskatchewan, pressure by government upon the College of Physicians was required to make the review process even minimally effective. But concern about over-servicing is not restricted to agencies of the government. One physician put it this way: "The Plan encourages the 'demoralization' of the physician. Inevitably when a doctor has a scheme that will pay for services rendered, including investigations, he will lean toward doing extra things and ordering extra tests to ensure that he is not missing something in the diagnosis. He is especially likely to overservice if, by so doing, he increases his income."

Escalating costs are a major concern; it is likely that the government will encourage the development of experimental modules to determine how the quantity of health care delivery might be increased and made more effective while at the same time reducing costs. These may include plans similar to health maintenance organizations currently being developed in this country.

It also seems likely that different ways of paying the physician will be tested. Thus far, the fee for service principle has been preserved as the usual basis for physician remuneration. One physician had this to say: "In Saskatchewan, nobody at the moment is thinking much about a salaried service. But the fee for service principle here and in the United States is in jeopardy because, in some instances, fees are not realistic. When a large third party pays fees, they take a much closer look than individual patients. Unless physicians in practice recognize this and permit adjustment of the fee structure, the fee principle will disappear." The words "experiments in capitation fees" and "experiments with salaried physicians" were heard in several places, but always somewhat *sotto voce.*

An important "lesson" may be learned from the stormy days of 1962 when the government of Saskatchewan and the College of Physicians and Surgeons of Saskatchewan were locked in what was seen as a battle for survival. At the height of this conflict communication between the combatants ceased and polarization of the general public was encouraged by both sides. It is testimony to the emotional stability and maturity of the people of Saskatchewan that so few signs of the battle remain. The need to maintain lines of communication between disagreeing groups is essential. Can we learn from the experience of Saskatchewan?

In restrospect, it is interesting to speculate as to why the government pushed ahead with plans to introduce the Medical Care Insurance Act with so little consultation with the physicians. Such

a course of action together with the controls over physicians proposed in the original legislation seemed certain to generate intense opposition by the physicians and to guarantee a major confrontation between the Saskatchewan government and the College of Physicians and Surgeons. Was this course of action accidental or deliberate? Was the confrontation planned so that the power of the College of Physicians and Surgeons to influence the shape of the health care system would be reduced? The College, by signing the Saskatoon Agreement, won several concessions from the government; but it also accepted that physicians in Saskatchewan henceforward would serve in and accept a compulsory, universal medical service plan administered by the provincial government. It is difficult to imagine the College agreeing to such an arrangement under any other circumstances than a major public confrontation.

Political history in this country indicates that social changes are brought about by "tinkering" with the system rather than by major confrontation. If a system of government-sponsored comprehensive health care is instituted, it will not occur without significant opposition from organized medicine. Will proponents of such a plan try to win the physicians' stronghold by scaling its walls and doing open battle as in Saskatchewan? Or will they try to take the bastion from the inside, little by little, program by program?

Opponents of government-sponsored comprehensive health insurance programs may say that "Americans would never accept socialized medicine." But Saskatchewan, Canada, is a territory adjacent to our own country and is inhabited by a people similar to us in many ways. In Saskatchewan since 1962 socialized medicine has been a popular and non-controversial part of the way of life. It is, however, hardly "what the doctor ordered."

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Refer to: Whiting WB, Beyer RD: The physician and workmen's compensation—A new paramedic to help with compensation cases (The Health Care Team). Calif Med 118:67-68, Mar 1973

The Physician and Workmen's Compensation

A New Paramedic to Help with Compensation Cases

WILLIAM B. WHITING, MD *and* ROBERT D. BEYER, MPA, *San Francisco*

The first social, no-fault, insurance legislation in California was the Workmen's Compensation Act of 1911. It has been changed and modified in the years since, and is having an increasing impact on the practice of most California physicians. Many physicians consider caring for the occupationally ill or injured time-consuming and difficult. A newly emerging kind of paramedic, the workmen's compensation benefit administrator, is available to assist the physician in overcoming difficulties encountered. A cooperative effort between the physician and the benefit administrator will expedite management of industrial patients.

THE INDUSTRIAL REVOLUTION caused dramatic changes in western life-styles. In addition to creating new kinds of employment, it led to a group of physically injured and disabled through industrial injuries and occupational illnesses. This effect was cause for great social concern and led, eventually, to the creation of workmen's compensation laws.

In 1911 New Jersey was the first state to successfully pass a compulsory workmen's compensation law. That same year nine other states, including California, passed such laws.[1] The last state to enact such legislation was Mississippi, in 1948.[2] Currently, a commission appointed by President Nixon is making a study of workmen's compensation as it now exists in the various states.[3]

From the California State Compensation Insurance Fund, 525 Golden Gate Ave., San Francisco.

Submitted February 24, 1972.

Reprint requests to: W. B. Whiting, MD, Medical Officer, California State Compensation Insurance Fund, 525 Golden Gate Ave., San Francisco, Ca. 94101.

The Compensation Law in California

The California Workmen's Compensation Act of 1911 has been added to and modified at many subsequent sessions of the legislature. It has maintained, through the years, two basic concepts: Legislative involvement in the delivery of medical

care by the private sector; and benefit provision, medical and social, at the employer's expense, irrespective of fault (no-fault). Provisions of the law include:

1. ". . . a liability on the part of all employers to compensate their employees for any injury incurred by the said employees in the course of their employment, irrespective of the fault of either party."[4]

2. ". . . adequate provisions for the comfort, health and safety and general welfare of any and all workmen and those dependent upon them for support . . ."[5]

3. ". . . full provision for . . . medical, surgical, hospital, and other remedial treatment . . ."[5]

These points have been interpreted by the courts and the Workmen's Compensation Appeals Board (WCAB) in the following manner:

1. A man's occupational illness or injury must be determined a result of his employment. ("The provisions . . . shall be liberally construed by the courts with the purpose of extending their benefits for the protection of persons injured in the course of their employment.")[6]

2. The employee or his dependents are entitled to temporary and permanent income benefits, as indicated.

3. Total medical benefits for the occupational illness or injury are to be provided without time limitations.

4. Life pensions must be provided to the occupationally ill or injured, if indicated.

5. All of the above benefits are to be provided by the employer and considered a portion of his overhead.

6. Consistent with the no-fault clause in the legislation, the employee is constrained from filing a negligence suit against his employer.

7. These benefits are not provided from tax revenues.

Physicians and Compensation Medicine

The California Labor Code, Section 3209.3, defines physicians as follows: "Physician includes physicians and surgeons, optometrists, dentists, podiatrists, and osteopathic and chiropractic practitioners licensed by California State law, and within the scope of their practice as defined by California State law."

Most physicians and surgeons serve populations in which there are persons subject to occupational illnesses and injuries. It is, therefore, inevitable that most practicing California physicians will become involved with the workmen's compensation claim for benefits, some of them as employers.

It is common for the treating physician to consider compensation cases difficult because they involve third parties (the employer or his representatives and members of the legal profession). Much of the difficulty in these cases can be averted through a cooperative relationship between the compensation insurance benefit administrator and the treating physician.

A New Paramedic

Compensation insurance benefit administrators are emerging as paramedics specializing in managing the third party relationships encountered in occupational illnesses and injuries. They are salaried employees of the State Compensation Insurance Fund. As the physician's assistant, the benefit administrator's primary responsibilities involve the social management of compensation claims. He will assist the physician in dealing with: (1) Employer involvement; (2) family relationships; (3) medico-legal problems; and (4) rehabilitation and return to work. The benefit administrator will aid the physician in the care of the patient as a whole. It is his responsibility to monitor the medical care delivered to the patient for its adequacy and to assure its quality. He also expedites medico-legal procedures associated with compensation claims.

Medical Reports and Compensation Claims

All medical reports on compensation claims are subject to legal interpretation. This medico-legal interface is a continuing source of problems in determining compensation benefits. Phrases that are perfectly clear, medically, may be given a completely different interpretation by the legal community. It therefore becomes imperative that the treating physicians acquire some proficiency in the techniques of compensation reporting. This is necessary if the patient is to obtain all of the benefits to which he is legally entitled.

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2. Personal communication with Malcolm R. Peattie, Deputy Director, California Department of Industrial Relations
3. This Commission to study States' Workmen's Compensation Laws was established by the Williams-Steiger Occupational Safety and Health Act of 1970
4. California Constitution, Article XX, Sec 21, adopted Oct 10, 1911
5. California Constitution, Article XX, Sec 21, adopted Nov 5, 1918
6. California Labor Code Section 3202 [69 (a)]

A "Second Generation" Stilbestrol Alert

A Memo to Physicians of California
from the
CMA Committee on
Pharmacy and Therapeutics

DURING THE LATE 1940's and early 1950's many physicians administered diethylstilbestrol to high-risk pregnant patients. Now the medical profession throughout the country is confronted with an association between maternal ingestion of this medication and the appearance of vaginal adenocarcinoma in female offspring years later.

This note is a reminder to physicians to consider paying particular attention to the offspring of diethylstilbestrol-treated patients to check for vaginal cancer, at least yearly. In addition, physicians should watch for and investigate promptly cases of irregular vaginal bleeding or other symptoms that can be due to an early malignant lesion, particularly in the young female population.

If any such cases are found, they should be treated promptly, and a report* of such cases should be made voluntarily to the State Department of Public Health, which is collaborating with the National Registry in Boston.†

*For report forms contact E. Fasal, MD, Bureau of Adult Health and Chronic Diseases, 2151 Berkeley Way, Berkeley, Ca. 94704, telephone (415) 843-7900, ext. 656.

†Registry for Clear-cell Adenocarcinoma (Mesonephroma of the Genital Tract in Young Women), Warren 275, 275 Charles Street, Boston, Mass. 02114; Arthur L. Herbst, MD, Director; Robert E. Scully, MD, Pathologist.

CLINICAL CARDIOLOGY SERIES

Treatment of Cardiogenic Shock

Part II

LAWRENCE S. COHEN, MD

Material Supplied by the American Heart Association

Assisted Circulation

AS INDICATED IN PART I of this review, the major abnormality in cardiogenic shock is failure of the left ventricle as an effective pump. Therefore considerable effort has been expended in the development of cardiac assist devices to help the left ventricle which has been damaged as a consequence of a myocardial infarction.

Many lessons concerning prolonged assisted circulation were learned from surgical procedures utilizing extracorporeal circulation. Although the heart-lung machine may take over completely the functions of oxygenation and pumping of blood, there are many limitations to this technique for patients in cardiogenic shock. The need for thoracotomy in a critically ill patient virtually rules out any potential efficacy of this approach. In addition, the problems of hemolysis, plasma protein changes, clotting, infection and post-perfusion lung make prolonged extracorporeal circulatory techniques unfeasible for patients with cardiogenic shock.

Modifications of total extracorporeal circulatory assist have been utilized as temporary measures to help support a failing circulation. Veno-arterial pumping is one of these modifications. With this method, blood is withdrawn through a cannula introduced into the central venous system from the femoral vein. Blood is pumped into the arterial system from the femoral vein. If the venous blood is passed through an oxygenator the patient is on

Part II of a two-part article. Part I appeared in the January issue.

Dr. Cohen is from Yale University School of Medicine, New Haven.

partial heart lung bypass for all practical purposes. If an oxygenator is not used, the procedure is much simpler but anticoagulant drugs still are necessary to prevent clotting within the system. It has been demonstrated that the lower body and extremities can tolerate prolonged periods of perfusion with venous blood.

Left Heart Bypass

This method of assisted circulation removes oxygenated blood from the left atrium and returns it to the systemic circulation. Flow to the left ventricle is thereby diminished by the amount removed from the left atrium. The pump is in series with the right ventricle and lungs but in parallel with the left ventricle. By reducing cardiac inflow the distended left ventricle is given some degree of rest. It is likely that myocardial oxygen consumption is diminished as end diastolic ventricular volume and radius are decreased. Left heart bypass may be accomplished with or without thoracotomy. In the context of a patient in cardiogenic shock, a method requiring thoracotomy is obviously not feasible. As an adjunct to post-operative care this method has been utilized with some success.

A method of left heart bypass which does not require thoracotomy has been developed. A transseptal cannula introduced into the external jugular vein is passed across the atrial septum into the left atrium. Although this method of cardiac assist was reported more than ten years ago, there is still no clinical trial demonstrating its efficacy for patients after a myocardial infarction.

Although any of the above mentioned forms of assisted circulation do reduce the flow work of the left ventricle, it has been demonstrated that myocardial oxygen consumption is much more closely related to pressure work. A method of assisted circulation that reduced the pressure work of the left ventricle would theoretically be of considerable benefit in reducing myocardial oxygen requirements.

Arterio-arterial pumping or counterpulsation is a form of assisted circulation that can reduce the systolic pressure against which the left ventricle must pump. In addition counterpulsation raises aortic diastolic pressure thereby increasing coronary bloodflow. In 1961 Harken et al reported on a counterpulsation device which involved cannulation of the femoral arteries. By synchronization with the electrocardiogram the pump aspirated blood from the femoral arteries during cardiac systole and returned blood to the central circulation during cardiac diastole. Considerable diastolic augmentation was achieved. Other investigators, using synchronized counterpulsation in dogs, found that myocardial oxygen consumption decreased by more than 20 percent and coronary bloodflow was increased by 50 percent.

A variation upon the method of counterpulsation is that produced by the use of an intra-aortic balloon. This technique involves the inflation of an intra-aortic balloon at the onset of diastole and its deflation at the onset of systole. The advantages of this method are that it is totally intravascular and no blood is handled outside the body. There is less hemolysis in this technique than in counterpulsation devices which depend upon aspiration and return of blood to the vascular system for their hemodynamic effects. Heparin must be used, however, because of clotting of blood around the balloon. Rupture of the balloon with introduction of gas emboli into the vascular system is a potential hazard. Damage to the aortic wall by overdistention of the balloon may occur. Although an arteriotomy must be made for introduction of the balloon into the vascular system, there is no need for the diversion of blood through a conduit of foreign material.

Because of the desirability of having a cardiac assist device which is completely non-invasive, counterpulsation utilizing external body compression has been a goal of several groups of investigators. Such a device could be applied quickly, be free of any extracorporeal handling of blood, have no need for anticoagulants and would not involve any operative intervention. Because of these features it might be available to a patient earlier in the course of cardiogenic shock before prolonged hypofusion of vital organs made survival unlikely. Counterpulsation of the extremities involves displacement of blood retrograde into the central aorta during diastole and increasing the capacity of the arterial system during systole so as to draw blood from the aorta.

Dennis and his associates utilized a pressure sleeve on the hindlimbs of dogs and applied synchronous counterpulsation. Osborn utilized a half-body pressure suit but this was found to be uncomfortable when applied to normal volunteers. Keith found similar results when human volunteers were utilized. Soroff and his associates have also evaluated external pressure suits with and without simultaneous external cardiac massage. The combination of external assist plus external

cardiac massage was more successful in resuscitating dogs that were in ventricular fibrillation than was external assist alone.

In 1968 a series of physiologic studies leading to the development of an external cardiac assist device called "the sequenced pulsator" was initiated by the author and several of his colleagues. The rationale of sequenced pulsation in contrast to nonsequenced external pulsation is based on theoretical considerations underlying the effect of externally applied pressure to varying sized vessels in the extremity. Large vessels with a low ratio of wall thickness to lumen collapse more readily in response to externally applied pressure than do smaller vessels which have a high ratio of wall thickness to lumen. A uniformly applied external pressure to an extremity during diastole would therefore be expected to collapse the larger, proximal vessels first, thereby impeding return of blood to the central aorta.

The sequenced pulsator consists of arm and leg sections which are divided into multiple zones, each of which may be individually and separately activated to externally compress the enclosed body tissue. Activation is accomplished by inflating a chamber in each zone with compressed air. Flexible hoses connect the pressure enclosures for the arms and legs to the pressure and timing controller. The electrocardiographic signal from the patient directs the sequenced inflation of the zones through a series of solenoid valves. At the onset of the QRS complex, all pressure is simultaneously evacuated from the extremity cuffs. With such a mode the heart will never pump against a pressure wave produced by the assist device. The onset of cuff inflation can be set manually according to the length of cardiac systole. At the onset of cardiac diastole the sequenced pressure inflation is begun. Inflating the cuffs at the beginning of diastole returns blood to the central circulation with a consequent rise in central aortic pressure. When the ventricle contracts there is diminished resistance in the periphery due to the previous empyting of arterial blood into the central circulation during the previous diastole. Sequenced pulsation has a milking effect upon the arterial and venous beds as pressure is applied sequentially from more distal to proximal sites. Although the sequenced pulsator has not yet been utilized in the therapy of patients in cardiogenic shock, the preliminary laboratory results indicate that external sequenced pulsation can augment cardiac output and aortic diastolic pressure.

Circulatory assist devices have the combined aim of decreasing left ventricular work and also of increasing coronary bloodflow. It is hoped that by so doing a severely damaged left ventricle may be able to compensate and take over from the support device. Since cardiogenic shock is likely to be self-perpetuating once prolonged hypoperfusion of vital organs occurs, earlier application of assist devices may help certain patients in cardiogenic shock. It must be recognized, however, that even with the early application of an assist device, ischemic areas of myocardium may progress to the stage of necrosis. Acute revascularization of the myocardium with a saphenous vein bypass graft may be helpful and necessary in selected cases. The role of the circulatory assist device in these instances will be to stabilize the patient's condition while diagnostic studies such as selective coronary arteriography are performed. The success of this approach will have to be assessed as experience with saphenous vein bypass grafting increases and the long range prognosis of the grafts becomes clearer.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BAGLEY, RICHARD OLIVER, Richmond. Died January 6, 1973 in Mazatlan, Mexico, aged 61. Graduate of the University of Colorado, School of Medicine. Denver, 1939. Licensed in California in 1942. Doctor Bagley was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association and an associate member of the American Medical Association.

BRUNER, CHARLES WILLIAM, San Diego. Died December 20, 1972 in San Diego, aged 59. Graduate of Rush Medical College, Chicago, 1938. Licensed in California in 1939. Doctor Bruner was a member of the San Diego County Medical Society.

D'ACQUISTO, GIUSEPPE, San Francisco. Died January 16, 1973 of heart disease, aged 50. Graduate of Regia Università degli Studi Palermo, 1948. Licensed in California in 1958. Doctor D'Acquisto was a member of the San Francisco Medical Society.

DIMITROFF, SIM P., Los Angeles. Died September 26, 1972 in Los Angeles of pneumonitis and septicemia secondary to multiple myeloma, aged 58. Graduate of the University of Michigan Medical School, Ann Arbor, 1939. Licensed in California in 1945. Doctor Dimitroff was a member of the Los Angeles County Medical Association.

DRAKE, HOWARD HILLIS, Auburn. Died September 10, 1972 of cancer, aged 64. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1934. Licensed in California in 1934. Doctor Drake was a member of the Placer-Nevada County Medical Society.

ENG, SAMUEL YEN, Los Angeles. Died November 6, 1972 in Los Angeles of Hodgkin's disease, aged 69. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Doctor Eng was a member of the Los Angeles County Medical Association.

FARRELL, LEO W., Sacramento. Died December 29, 1972, aged 76. Graduate of St. Louis University School of Medicine, 1923. Licensed in California in 1923. Doctor Farrell was a retired member of the Sacramento County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

GRAHAM, HAROLD L., Capitola. Died October 12, 1972 of complications of leukemia, aged 77. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1939. Licensed in California in 1939. Doctor Graham was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

HICKEY, N. GLENN, Downey. Died December 17, 1972 in Lynwood of heart disease, aged 71. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1934. Licensed in California in 1934. Doctor Hickey was a member of the Los Angeles County Medical Association.

IVEY, EVERETT D., Oakland. Died January 21, 1973 in Oakland of myocardial infarction, aged 78. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1923. Licensed in California in 1926. Doctor Ivey was a member of the Alameda-Contra Costa Medical Association.

KIRSCH, RALPH LOUIS, Del Mar-San Diego. Died November 24, 1972, aged 86. Graduate of the University of Minnesota Medical School, Minneapolis, 1912. Licensed in California in 1924. Doctor Kirsch was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

KNOUF, EVELYNNE G., Pasadena. Died January 9, 1973 in Glendale, aged 62. Graduate of University of Southern California School of Medicine, Los Angeles, 1937. Licensed in California in 1937. Doctor Knouf was a member of the Los Angeles County Medical Association.

KRAEMER, HORST CHARLES, Laguna Hills. Died August 29, 1972 of cardiac arrest and carcinoma of the lung, aged 70. Graduate of Albertus-Universität Medizinische Fakultät, Konigsberg, Germany, 1927. Licensed in California in 1940. Doctor Kraemer was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

LA DAGE, LEO H., Long Beach. Died November 12, 1972 in Long Beach of Australia antigen hepatitis, aged 72. Graduate of State University of Iowa College of Medicine, Iowa City, 1927. Licensed in California in 1943. Doctor La Dage was a member of the Los Angeles County Medical Association.

LEGGETT, ELIZABETH A., Laguna Hills. Died July 31, 1972 of heart disease, aged 74. Graduate of the University of Minnesota Medical School, Minneapolis, 1928. Licensed in California in 1933. Doctor Leggett was a retired member of the Orange County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

MacLean, Hugh Gordon, Oakland. Died December 28, 1972 in Oakland of heart disease, aged 76. Graduate of Oakland College of Medicine and Surgery, 1917. Licensed in California in 1917. Doctor MacLean was a past president of the California Medical Association, a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Morris, Francis Joseph, Los Angeles. Died December 8, 1972 in Los Angeles of arterial cerebral vascular sclerosis, aged 77. Graduate of Rush Medical College, Chicago, 1923. Licensed in California in 1926. Doctor Morris was a member of the Los Angeles County Medical Association.

Ordway, George Lewis, Mill Valley. Died December 18, 1972, aged 53. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1949. Licensed in California in 1949. Doctor Ordway was a member of the Marin Medical Society.

Parker, Leon O., San Francisco. Died January 13, 1973 in San Francisco, aged 71. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1926. Licensed in California in 1929. Doctor Parker was an associate member of the San Francisco Medical Society.

Smith, Joseph Raymond, Fresno. Died December 28, 1972 in Fresno, aged 67. Graduate of the Medical College of South Carolina, Charleston, 1933. Licensed in California in 1934. Doctor Smith was a member of the Fresno County Medical Society.

Stewart, Blaine B., Fresno. Died December 30, 1972, aged 51. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1955. Licensed in California in 1956. M.D. Degree from California College of Medicine, 1962. Doctor Stewart was a member of the Fresno County Medical Society.

Stuurmans, Sheldon Harry, Los Angeles. Died August 20, 1972 of arteriosclerotic cardiovascular disease, aged 74. Graduate of the University of Minnesota Medical School, Minneapolis, 1925. Licensed in California in 1941. Doctor Stuurmans was a member of the Los Angeles County Medical Association.

Swett, Wilber F., San Francisco. Died January 11, 1973 in Palo Alto, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1922. Licensed in California in 1922. Doctor Swett was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Totherow, William Roy, Valencia. Died December 31, 1972, aged 51. Graduate of Harvard Medical School, Boston, 1951. Licensed in California in 1957. Doctor Totherow was a member of the Los Angeles County Medical Association.

Tuveson, Gerry R., Oakland. Was killed January 10, 1973 in the crash of a light plane in Mono County, aged 36. Graduate of University of Illinois College of Medicine, Chicago 1961. Licensed in California in 1970. Doctor Tuveson was a member of the Alameda-Contra Costa Medical Association.

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BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

ULTRASTRUCTURE OF BONE AND JOINT DISEASES—Kazushi Hirohata, MD, Associate Professor, Department of Orthopedic Surgery, Kobe University School of Medicine, Kobe, Japan; and Kazuo Morimoto, MD, Instructor, Department of Orthopedic Surgery, Kobe University School of Medicine, Kobe, Japan. Igaku Shoin Ltd., Toyko, Publisher; Distributed by Grune & Stratton, 111 Fifth Avenue, New York, N.Y. (10003), 1971. 339 pages, $35.00.

Orthopedic surgeons Kazushi Hirohata and Kazuo Morimoto have put together a beautiful volume dealing with the ultrastructure of tissues involved in diseases of the bone and joint. The opportunity to be precise in sampling tissues for electronmicroscopy is perhaps open to only the astute surgeon. The authors have taken advantage of this. The electronmicrographs are prepared from tissue specimens obtained at the time of surgery. They are thus able to pinpoint the location of many of the specimens in relation to the diseased area. This is of course essential in interpreting the findings of a disease such as osteoid osteoma which may present with an entirely different picture just a short distance away.

In their book, observations made at the ultrastructural level are accompanied by brief notes on the clinical history of the patient, by light microscopic findings, and occasionally, by photographs of the gross specimens and of roentgenographs. This arrangement places the electronmicrographs in proper perspective for readers unfamiliar with the field.

A major criticism has to be that the legends are too concise. Since the electronmicrographs are by no means self-explanatory and show only a tiny fraction of what the authors must have observed, much valuable information is thereby withheld from the reader. Minor defects such as a few unlabeled micrographs (e.g., Fig. 271 p. 240), the usage of unorthodox terms (e.g., "regressive cell" for degenerating or necrotic cell p. 139) and a few grammatical errors, do not detract from the generally good quality of the printing. The reference list of 307 include all the major works and would be of use to anyone cultivating an interest in this rather small field.

This volume will be a valuable compendium for the student of bone and joint disease. As the authors note "Even minor morphological changes in cells and cell matrices would be of significance to the respective diseases." Significant indeed!

ANTHONY C. SHEN, MD
EPHRAIM P. ENGLEMAN, MD

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PROGRESS IN HEMOSTASIS AND THROMBOSIS—Volume I—Theodore H. Spaet, MD, Head, Hematology Division, Montefiore Hospital and Medical Center; Professor of Medicine, Albert Einstein College of Medicine, Bronx, N.Y., Grune & Stratton, Inc., 111 Fifth Avenue, New York, N.Y. (10003), 1972. 257 pages, $15.00.

This book represents the first of a series of monographs to be devoted to various current topics in blood coagulation and thrombosis. It is appropriately dedicated to the memory of Dr. Paul Aggeler, one of the great physician-investigators of our time who practiced many years in San Francisco and discovered factor IX (PTC). The contributors to this volume have all worked in the particular area on which they write and this is reflected in authoritative and up-to-date reviews. Indeed, in all the papers one can find references cited which were in press at the time the book was published. The first chapter describes the modern view of the coagulation mechanism and is authored by Drs. Yale Nemerson and Fran Pitlick, who have made notable contributions in this area. The second chapter is on the molecular basis of hereditary clotting disorders and is by Dr. Oscar Ratnoff, who with Dr. Zimmerman made the important discovery that cross-reacting material to factor VIII is present in all hemophilic patients but decreased in patients with von Willebrand's disease. The third article is by Drs. Feinstein and Rapaport on the acquired inhibitors of blood coagulation; it is clearly written and informative and contains many original concepts and thoughts. The important clinical problem of bleeding in uremia is discussed by Dr. Rabiner. The remaining articles are devoted more to thrombosis than blood coagulation and will be of particular interest to cardiovascular surgeons, radiologists and others who are seeking non-thrombogenic surfaces or materials. All the chapters are beautifully illustrated and this is a book which every practicing hematologist will find useful. It can also be strongly recommended to all those who are interested in problems of experimental thrombosis.

CECIL HOUGIE, MD

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SURGERY OF THE ELBOW—Second Edition—Frederick M. Smith, MD, Former Associate Attending Orthopedic Surgeon, Presbyterian Hospital, New York Orthopedic Hospital and Vanderbilt Clinic. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1972. 340 pages with 154 illustrations, $14.00.

The author has made an excellent contribution to the handling of traumatic and other lesions of the elbow which is one of the more complicated and often injured of all joints. He indicates the value of it for residents in traumatic and orthopedic surgery. This writer also recommends it as a reference and for review, not only for the resident in training but for the surgeon doing traumatic work as well as the orthopedist, whether seeing a lot or only an occasional case of elbow injury.

General basic sound principles of treatment are well described, including the "when" and "how" of reduction, immediate post-reduction care, signs of danger to watch for, time period of healing and the important rehabilitation of the part, all of which although somewhat elementary, deserve a review from time to time for surgeons being confronted with these common and at times definitely hazardous conditions.

Pitfalls and complications of the various types of injury to bones, joints and soft tissue, as well as those of different forms of treatment including both closed as well as open methods, are well presented. Also a good discussion is given referable to the avoiding of late complications and if these develop or are encountered methods of treating same are reviewed.

PAUL E. MCMASTER, MD

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MENTAL RETARDATION—Volume IV—An Annual Review—Edited by Joseph Wortis, MD, Director of Developmental Services and Studies, Department of Psychiatry, Maimonides Medical Center, Brooklyn, N.Y., Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1972. 234 pages, $15.75.

This is the fourth volume of this annual series devoted to recent developments in mental retardation. Topics covered include: clinical aspects; parent counseling; parents as teachers of their own children; some recent trends; a parent's view; genetics; psychopharmacology; neurology; neurophysiology; audiology; federal legislation and finally an interesting survey of recent Italian literature devoted to mental retardation.

In general the articles are well written and enhanced by good, up-to-date bibliographies. Most illuminating were the articles on parent counseling by Helen Wortis

and one by Nanette Doernberg on parents as teachers of their own children. Equally helpful was the fine survey on recent trends in neurophysiology by Robert Ellington. This is not to say that the other articles were not equally competent but my own personal bias obviously plays a part in selecting these articles for special mention.

Errors were few and not worthy of mention. However, the statement on page 209 is open to question. If Italy, with a population of 53 million, has 3 million retardates she has an incidence of 6 percent which seems too high. What makes all of this even more dubious is the statement that "one million retardates are below the age of one year."

Unfortunately almost every article covers subjects that are already more than adequately discussed elsewhere. This dilemma in the midst of a publication explosion is one that faces workers in all fields of human endeavor. I do not have a solution but possibly the editor could use this review to stress certain aspects of mental retardation not dealt with adequately elsewhere. Despite this the editor is to be congratulated on his efforts and it is hoped this series will be continued and improved.

MARIO VALENTE, MD

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FOOD ALLERGY—Its Manifestations and Control and the Elimination Diets—A Compendium—Albert H. Rowe, MD, Lecturer in Medicine (Emeritus), University of California School of Medicine, San Francisco; Allergist, Samuel Merritt Hospital, Oakland, California; in collaboration with Albert Rowe, Jr., MD, Department of Medicine, Highland Hospital and Samuel Merritt Hospital, Oakland. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. (62703), 1972. 687 pages, $20.00.

The senior author, Albert H. Rowe, died October 29, 1971. He was widely known for his emphasis on food allergy, its manifestations and control by elimination diets. This volume, as indicated in the title is "A Compendium" of his work in this field for over forty years. Nowhere can a reader find more detailed information on this subject than in the present volume where this topic is covered completely and with a lucidity characteristic of the two Doctors Rowe, Senior and Junior.

Although food allergy is stressed throughout the volume, there are adequate discussions of inhalant (especially pollen) drug, and infectant allergy. The allergic diseases commonly encountered in clinical practice are described in full and the established methods of diagnosis and treatment are delineated. The book is complete in every respect even to an exceptionally fine bibliography. This work is a fitting testimonial to the elder Dr. Rowe. It is one of the better modern texts on allergy and is highly recommended to all students of medicine and practitioners of the art.

M. COLEMAN HARRIS, MD

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CLINICAL PHARMACOLOGY—Basic Principles in Therapeutics—Edited by Kenneth L. Melmon, MD, Associate Professor of Medicine and Pharmacology and Chief, Division of Clinical Pharmacology, University of California, San Francisco, School of Medicine; and Howard F. Morrelli, MD, Associate Professor of Medicine and Pharmacology, and Vice Chairman (House Staff Affairs), Department of Medicine, University of California, San Francisco, School of Medicine. The Macmillan Company, 866 Third Avenue, New York City (10022), 1972. 718 pages, $16.00. Available in paperback, $11.95.

The achievement for which Drs. Melmon and Morrelli deserve commendation is described by them in the Preface: "Successful use of this book requires knowledge of both pharmacology and medicine. It does not replace the basic textbook in either discipline; rather, it is a supplement to both. Unit II does not include all, or even most, of the important diseases or drugs that might be discussed. The approach described in each chapter—physiology, pathophysiology, pharmacology, and, finally, the integration of these subjects—is consistent, can be applied at the bedside, and constitutes what the editors consider to be active clinical pharmacology." The text is a rich source of clinically applicable information on pharmacology and pathophysiology.

There are four sections: I. Basic Principles of Drug Administration. Included in this section are a review of procedures and mechanisms of therapeutic investigation leading to rational therapy, and a discussion of criteria for evaluation of the literature on therapeutics. A superb summary of factors determining the absorption, metabolism and disposition of drugs affecting the decision of dosage regimen concludes the Unit. II. Pathophysiologic and Pharmacologic Considerations in Drug Administration. The approach is oriented toward the pathophysiology of disease leading naturally to discussion by systems. A large group of disorders of the renal, hepatic and gastrointestinal, respiratory, endocrine, and hematopoietic systems are reviewed in the light of physiologic concepts and treatment developed with emphasis on relevance to these concepts. Additional categories include inflammatory disorders, infectious disease, psychiatric and neurological disorders, disorders of cell growth and genetic disorders. Every effort is made to relate treatment to physiology to establish rationale and relevance. Useful treatment that is empirical is properly identified. III. Recognition and Evaluation of Effects of Drug Administraton. Unrecognized measures including placebo, drug reactions, drug interactions, treatment of drug overdosage and a delightful chapter on "Drug Models of Disease: Sweet Uses of Adversity" complete the text. This section is one of the best and most succinct of the available reviews of the subject of drug reactions and interactions. IV. Clinical Examples of the Use of Drugs. Programmed cases in therapeutics illustrate the principles developed throughout the book. I found the unit a bit complicated and tedious. In revision, it would be well to simplify the discussion.

References are numerous and pertinent, greatly increasing the value of the book. The index is adequate.

Although the book is designed to develop basic principles and is not meant to be an inclusive text on treatment, the overt omissions leave one with a feeling that the book is incomplete. Some contradictions exist between chapters and a few errors exist in tables of dosage of drugs.

In the time between final draft and publication, new drugs have been approved and in some diseases the treatment of choice has changed. But this is a particularly difficult problem for editors and publishers of texts with many authors.

Of the authors, nine are on the staff of the University of California in San Francisco and ten are from other institutions. There is evident a breadth of clinical competence and experience which fulfills the title "Clinical Pharmacology."

As with all books produced by multiple authors, there is some unevenness in presentation, and for me, a few attempts at humor were out of place.

Throughout the text some Principles are stated in boldface type. Often these statements are pithy, germane and serve to emphasize important points. Some, however, seemed superfluous and condescending and were annoying.

"Clinical Pharmacology" is recommended for all who use pharmacological agents in treatment of adults. The deficiencies and omissions referred to above do not detract materially. It should be accompanied by a good text of pharmacology and a sustained interest in keeping up with current information on treatment of individual diseases.

MARCUS A. KRUPP, MD

Refer to: Atkinson RM: Importance of alcohol and drug abuse in psychiatric emergencies. Calif Med 118:1-4, Apr 1973

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Importance of Alcohol and Drug Abuse in Psychiatric Emergencies

ROLAND M. ATKINSON, MD, *Orange*

THE GREAT VARIETY of acute medical and behavioral disorders related to drug and alcohol abuse, and the need for prompt recognition of abuse in the diagnosis and treatment of these disorders, are matters by now well known to most physicians. Not only widespread abuse but also recent changes in California law and public institutional practices —for example, repeal of the penal code statute making acute alcohol intoxication a criminal act, and the recent shift toward community-based, ambulatory treatment of mentally disordered patients formerly sent to state hospitals—have created circumstances in which all physicians may expect increasingly frequent encounters with acutely disturbed patients whose problems are related in some way to intoxication with alcohol or other drugs, in office practice and, especially, in the emergency room setting.

In view of these trends, data on the prevalence and nature of acute problems related to intoxication, particularly behavioral or psyschiatric problems, should be valuable not only to psychiatrists but to all practitioners. Somewhat surprisingly, not many surveys of the role of drug and alcohol abuse in psychiatric emergencies have been published.[1-3]

In this report, data are presented on the physician-rated frequency and relative importance of drug and alcohol abuse in 503 adult and adolescent emergency cases evaluated at the Psychiatric Emergency Admitting Unit (EAU), UC Irvine-Orange County Medical Center. I sought answers to these three questions.

1. How frequently and to what degree are alcohol and drug abuse judged to be relevant to emergency cases?

2. Is there a correlation between abuse and severity of the emergencies?

3. How accurately do formal psychiatric diagnoses reflect the frequency of abuse in the presenting episodes?

Setting

The EAU combines most elements essential to a discrete, comprehensive psychiatric emergency service;[4] its organization has been described in detail elsewhere.[5] The Medical Center is located centrally within Orange County, and serves a broad range of patients, predominantly from Caucasian, lower middle-class groups, from adjacent

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urban and residential districts. The EAU, open around the clock, is the only facility of its kind within the county, and, therefore, it receives referrals from many sources, especially during evening and week-end hours. Hence the following are rather common referral agents: All elements of the county's Community Mental Health Service system; county Sheriff's Department and the police forces of all cities within the county; jails, the Juvenile Probation Department, and all court jurisdictions; the medical-surgical emergency room of the county hospital and all private hospitals in the area; private practitioners; social agencies. There are also walk-ins by families and individuals. While no claim can be made that patients seen are representative of psychiatric emergencies in general, it is likely that our patients represent a broader socio-economic range than might be found in an emergency clinic serving a central city or an entirely suburban population.

Each patient who presents with serious signs of chemical intoxication is evaluated in the medical-surgical emergency room before referral to the EAU, which is physically and administratively separate. At the EAU, he is examined by a first-year or second-year psychiatric resident. The arrangement of the unit makes it possible for observation and evaluation to be extended over periods up to three days. Repeated psychiatric examinations by the housestaff and the attending psychiatrist in charge of the unit are commonplace.

Method

Psychiatric houseofficers completed a research questionnaire on 503 of the 511 consecutive EAU patients admitted during October, 1971. One item asked them to judge on a six-point scale the relevance of alcohol use (A) to the present emergency episode: 0 = unrelated; 1 = use of alcohol by another person may be related, but not use by the patient; 2 = use by patient could possibly be related to the episode; 3 = use probably related, but only secondarily; 4 = use is important factor in episode, along with other factors; and 5 = use is the single most important factor. Housestaff were asked to make a similar judgment for relevance of drug use (D) to the present episode. Drug use here excluded proper use of prescription and over-the-counter drugs, and intentional overdosage to produce self-injury with a drug not otherwise abused. *Some degree* of abuse was indicated by an A and/or D rating of 1 or above. Abuse was considered a *minor factor* in the emergency if neither the A nor D rating was higher than 3. Abuse was considered a *major factor* if the A and/or D rating was 4 or 5.

TABLE 1.—*Case-by-case Distribution for A and D Ratings Showing Number of Patients in Each Category (See Text for Rating Definitions)*

Degree of relevance of Drug abuse (D)	Degree of relevance of Alcohol abuse (A)						
	0	1	2	3	4	5	Total
0	*233	4	22	14	38	25	336
1	3	1	1	1	0	0	6
2	19	0	2	1	3	4	29
3	13	1	0	3	1	1	19
4	24	0	4	2	17	0	47
5	48	1	3	1	6	7	66
Total	340	7	32	22	65	37	503

*Number of patients in each category

Housestaff also rated globally the degree of acute psychiatric impairment (IMP), based on admission mental status alone. The rating was on a seven-point scale: 0 = normal, no impairment; 1 = borderline impairment; 2 = mild; 3 = moderate; 4 = marked; 5 = severe; and 6 = among the most extremely impaired patients.

Psychiatric diagnoses (DX) were obtained from the EAU log, where admission differential impressions are recorded and later transcribed for hospital statistical use. These were reduced to nine categories: *Abuse* = all diagnoses suggesting relationship of the disorder to alcohol and/or drug abuse—that is, alcoholism, drug dependence, organic brain syndromes related to drugs or alcohol; schizophrenia; transient situational disorders; neuroses; personality disorders, excluding those related to alcohol and drug abuse; affective disorders; brain syndromes, excluding those related to alcohol and drug abuse; normal (no mental disorder); and other, which included all other diagnostic categories, including "deferred," blanks and questionable cases.

IMP and DX were nearly always based on impressions written after initial, preliminary evaluation. A and D ratings, on the other hand, were based on the total work-up, which varied from the preliminary study alone to more thorough evaluation over hours to days.

Results

Frequency and relevance of abuse. Some degree of alcohol and/or drug abuse was judged relevant in 270 cases (53 percent). Drug abuse alone was implicated in 107 cases (21 percent), alcohol alone in 103 (20 percent), and mixed alcohol and

TABLE 2.—*Acute Impairment (See Text for Category Definitions)*

IMP Category	Total Sample No. of Cases	Abuse Subset Some degree*	Abuse Subset Major factor*
0	65	31	18
1	75	45	31
2	89	60	40
3	123	65	42
4	85	35	26
5	55	27	22
6	11	6	5
Totals	503	269†	184†

IMP—Acute psychiatric impairment

*"*Some degree*" includes "*Major factor*" and "*Minor factor*" cases.

†IMP data for one case of major-factor abuse was lost.

TABLE 3.—*Initial Diagnoses (See Text for Category Definitions)*

Category	Total Sample No. of Cases	Abuse Subset Some degree*	Abuse Subset Major factor*
Abuse	124	120	110
Transient situational disorders	95	50	27
Schizophrenia	89	26	7
Neuroses	52	21	10
Personality disorders	42	17	9
Affective disorders	20	4	2
Organic brain syndromes	19	4	4
Normals	13	4	0
Other	52	24	16
Totals	506†	270	185

IMP—Acute psychiatric impairment

*"*Some degree*" includes "*Major factor*" and "*Minor factor*" cases.

†Data on diagnostic impression (from log) available in 3 cases where questionnaire data on D, A and IMP were not available.

drug abuse in an additional 60 (12 percent). Abuse was a *major factor* in 185 cases (36 percent). Of these, pure drug abuse was implicated in 72 (14 percent), alcohol in 63 (12 percent), and mixed abuse in 50 (10 percent). The numbers of patients in each category are given in Table 1.

Relation of abuse to severity of impairment. There were no appreciable differences in frequency of drug and alcohol abuse across IMP categories. The percentage of patients in each category for whom *some degree* of abuse was implicated are as follows (moving from IMP category 0 to 6): 48 percent, 60 percent, 67 percent, 53 percent, 41 percent, 49 percent and 54 percent. A similar pattern emerged for percentage of cases in which abuse was judged to be a *major factor:* 28 percent, 41 percent, 45 percent, 34 percent, 31 percent, 40 percent and 45 percent. Table 2 shows the number of patients in each category.

Relation of abuse to diagnosis. Abuse preliminary diagnoses were given in 124 cases (24 percent). Of these, 120 were "true-positive"—that is, backed up by positive A and/or D ratings. Thus *abuse* diagnoses, although the most frequent diagnostic category, accounted for just 120 of 270 cases (45 percent) in which *some degree* of abuse was judged relevant to the emergency. In cases where abuse was judged a *major factor, abuse* diagnoses accounted for 110 of 185 cases (59 percent). In cases where abuse was judged a *minor factor, abuse* diagnoses accounted for only 10 of 85 cases (12 percent).

The remaining cases in which abuse was implicated were distributed over all diagnostic categories. The percentage of abuse-related cases within each diagnostic category is given next: schizophrenia, 29 percent; transient situational disorders, 53 percent; neuroses, 40 percent; personality disorders, 40 percent; affective disorders, 20 percent; brain syndromes, 21 percent; normals 31 percent; and other, 46 percent. Table 3 shows the number of patients in each category.

Discussion and Conclusions

Some of these findings confirm those of the only comparable survey in the recent psychiatric literature. Trier and Levy[3] asked physicians at another California county hospital to rate presence of drug or alcohol "addiction" independent of diagnosis in 174 consecutive emergency cases. Addiction was not defined. Half the cases were rated as addiction-related: 35 percent alcohol and 15 percent drugs. There was no rating category for mixed alcohol and drug addiction. The proportions did not vary with degree of severity of the emergency. Muller, Chafetz and Blane,[1] reporting on four separate surveys, showed a range of 4 percent to 26 percent alcohol-related diagnoses among psychiatric emergencies. They also demonstrated that "drinking" as a contributing factor in the emergency was more frequent than alcohol-related diagnoses, and was distributed among all diagnostic groups. Their work, reported before the drug abuse explosion, did not categorize drug abuse at all.

Data in this report show that drug and alcohol abuse were judged to be relevant to emotional and behavioral states leading to emergency evaluation in more than half the cases seen in a busy general psychiatric emergency service. Abuse figured prominently in cases of every degree of severity

and in every major diagnostic category. Drug and alcohol abuse-related initial formal diagnoses missed over half the cases in which abuse was judged relevant on a special research instrument.

Findings of this survey support several important assertions. For psychiatrists and other physicians working primarily in a specialized psychiatric emergency service setting, drug and alcohol abuse must be reckoned with as one of the most important and prevalent categories of the circumstances precipitating emergency room entries. For physicians with important responsibilities in the development of drug and alcohol abuse intervention programs, the findings indicate that the general psychiatric emergency service is a strategic location for drug and alcohol abuse case finding, intervention and referral, more so than may be generally recognized from superficial surveys of formal diagnoses alone. All practitioners should be aware that when patients present with urgent or acute emotional or behavioral problems, drug or alcohol abuse may be an important precipitating factor in the onset of the problem, even in circumstances where the presenting signs and symptoms suggest a psychiatric disorder which does not typically imply such abuse.

Confirmation of an abuse problem in a patient experiencing a sudden, severe behavior disorder, of course, requires something beyond a high index of anticipation or suspicion. While some patients volunteer information about their abuse of alcohol or drugs, and others "confess" when confronted by the examiner's impression that abuse may be involved, still others may deny the fact or may be too disturbed for coherent interviewing. In such cases routine interviewing of persons who may have accompanied a patient to the examination is helpful. Clinical laboratories in a number of locales now make available a rapid, low-cost, qualitative serum or urine screening procedure which may identify the presence of any of several dozen drugs of abuse. These examinations may be indispensable where a good history is lacking, and the availability of such a laboratory procedure to every sizable emergency facility is to be encouraged.

Acknowledgement

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Refer to: Teberg A, Hodgman JE: Congenital syphilis in newborn.
Calif Med 118:5-10, Apr 1973

Congenital Syphilis in Newborn

ANNABEL TEBERG, MD *and* JOAN E. HODGMAN, MD, *Los Angeles*

In six cases of congenital syphilis in newborn at Los Angeles County-USC Medical Center over a seven-month period the clinical findings fell into two categories related to the time of onset of symptoms. Infants ill in the nursery presented evidence of transplacental infection; infants who became ill later showed the "classic" findings of rash, rhinorrhea and pseudoparalysis.

No single clinical symptom was present in all cases but all symptomatic infants had radiographic evidence of bone disease. Respiratory distress was present at the onset of symptoms in three of four infants with neonatal disease, and all three had evidence of interstitial pneumonia in chest radiographs.

Serologic testing may be difficult to evaluate in the newborn period, but more recent and specific tests are helpful in diagnosis. Penicillin remains the drug of choice. The only death occurred at five hours of life in a premature infant. Growth and development in surviving infants appeared normal.

DURING THE PAST DECADE, the reported incidence of syphilis in the United States has risen sharply.[1,2] The increase in congenital syphilis has paralleled that of adult cases. Brown et al[3] estimated there were twice as many cases of congenital syphilis in 1962 as in 1957. The Los Angeles County-University of Southern California Medical Center has experienced a similar rise in incidence. In the seven-month period from October, 1968, to May, 1969, six cases of congenital syphilis were treated, as against three in the previous 12-month period.

The six recently treated cases are reported to illustrate the wide range of clinical symptoms seen in early infancy. In four of the infants the condition was diagnosed shortly after birth. The two remaining patients were discharged asymptomatic from the nursery and returned with symptoms when two to three months of age.

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Submitted June 27, 1972.

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We are grateful to Zack Haddad, MD, Assistant Professor of Pediatrics and Director of Pediatric Allergy and Immunology of the Los Angeles County-University of Southern California Medical Center for his assistance in performing the IgM serum level laboratory tests. The specific IgM FTA-ABS tests were performed through the courtesy of William J. Brown, MD, Chief, Venereal Disease Branch of the National Communicable Disease Center.

TABLE 1.—*Results of Serologic and Immunologic Tests on Infants and Mothers*

Case	Maternal Serum Level at Delivery		Infants' Serum Level at Birth					
					IgM	FTA-ABS		
	Kolmer*	VDRL	Kolmer	VDRL	mg/100 ml	γG	γA	γM
1	32	Reactive	32	Reactive	290	Reactive + + + +	Nonreactive	Reactive + + +
2	32	Reactive	128	Reactive	150	Reactive + + + +	Reactive + +	Reactive + + + +
3	128	Reactive	128	Reactive	..	Reactive + + + +	Nonreactive	Reactive + + +
4	64	Reactive	128	Reactive	..	Reactive + + + +	Reactive +	Reactive + + + +
5	128	Reactive	128	Reactive	..	..	..	..
6	64	Reactive	128	Reactive	..	..	..	..

*Reciprocal of final dilution.

TABLE 2.—*Summary of Clinical Data in Six Cases of Congenital Syphilis*

Case	Respiratory Distress	Hepato-megaly	Spleno-megaly	Jaundice	Lymph-adenopathy	Hemolytic Anemia	Packed cell volume %	Rash	Rhinitis	Pseudo-paralysis
1	+ + +	+ +	+ +	+	0	+	43	0	0	0
2	+	0	+ +	0	+	0	50	0	0	0
3	0	0	0	0	0	0	52	0	0	+
4*	+ + +	+ + +	+ + +	0	0	+	36	0	0	0
5	0	0	0	0	0	+	26	+	+	+
6	0	0	+ + +	0	0	+	24	+	0	+

*Died at five hours of life.

Reports of Cases

CASE 1: A girl, birth weight 2,960 grams, gestational age 34 weeks (above the 90th percentile; Denver Intrauterine Growth Curve[4] [I.U.G.C.]), was born to a 34-year-old Mexican-American (M-A) woman, gravida 9, para 8. Pregnancy was uneventful with the exception of a mild episode of "flu-like" illness with rash lasting 15 days during the last month of pregnancy. A Venereal Disease Research Laboratory (VDRL) serologic test for syphilis on blood drawn in the first trimester of pregnancy was positive but the mother was lost to public health follow-up.

At birth the infant was depressed, with an Apgar score of 5, and a heart rate of 80. In the nursery, she was cyanotic and had grunting, rapid respirations. The liver was palpable 4 cm below the right costal margin and the spleen 2 cm below the left costal margin. The extremities were moderately edematous and the face was puffy. There was a left facial palsy and left upper arm weakness. A radiograph of the chest showed a diffuse infiltrate in the right lung field and questionable cardiomegaly. Kolmer and VDRL tests performed on cord blood were positive (Table 1). The infant was given fluids intravenously and penicillin and digitalis parenterally. On the second day, a generalized fine petechial rash developed over abdomen and back. There were large ecchymotic areas, and bleeding around vena puncture sites. Visible jaundice appeared with a total bilirubin of 5.3 mg per 100 ml, of which 1.2 mg was direct. Clinical findings are summarized in Table 2. Radiographs of the long bones showed the typical lesions of congenital syphilis. The patient remained severely ill, requiring supplemental oxygen and parenteral fluids for six days, then gradually improved. Penicillin and digitalis were discontinued at two weeks of age, and the infant was discharged from the nursery in good condition at three weeks of age.

When last seen, at two months of age, the baby was alert and active. No residual neurological or physical abnormality was evident. The mother returned to Mexico and the infant was lost to further follow-up.

CASE 2: A girl, birth weight 2,330 grams, gestational age 38 weeks (10th to 25th percentile I.U.G.C.), was born to a 25-year-old M-A woman, gravida 3, para 2. Pregnancy history was normal. The mother had had one prenatal clinic visit in the first trimester and a VDRL test on a speciman drawn at that time was negative. At birth, the infant had a wrinkled appearance, decreased subcutaneous fat and generalized poor muscle tone. On the fifth day she became tachypneic, the respiratory rate rising to 100. At this time the spleen was palpated 2 cm below the left costal margin and small shotty lymph nodes were felt in the left axilla. Radiographs of the chest revealed a diffuse infiltrate in the right lung field. Radiographs of the long bones showed changes consistent with congenital syphilis. Kolmer and VDRL tests on cord blood were positive (Table 1). Before these results were available, parenteral kanamycin and ampi-

cillin were given, with clinical improvement. The baby was discharged from the nursery on completion of two weeks of this therapy.

When last seen, at three months of age, she was alert, gaining well and developing normally. Radiographs of long bones at this time showed healing of the destructive bone lesions.

CASE 3: A girl, birth weight 2,950 grams, gestational age 40 weeks (25th to 50th percentile I.U.G.C.), was born to a 23-year-old M-A woman, gravida 2, para 1. The mother had had no prenatal care and was admitted to the hospital in active labor. Pregnancy was normal. The infant had peeling skin and meconium-stained nails and umbilical cord. She had generalized poor muscle tone, a weak grasp reflex and an incomplete and sluggish Moro reflex. There was shortening of the right leg and click on rotation of the right hip. Radiographs of the bones showed the classic changes of congenital syphilis, with lesions in the acetabulum and right femur. The spinal fluid was clear, contained a very few round cells and had protein content of 113 mg per 100 ml and sugar of 45 mg per 100 ml. The infant was treated with parenteral penicillin and was discharged at two weeks of age.

When last seen, at three months of age, she was alert, active and growing well. The right leg remained shorter than the left with limitation of movement. Radiographs showed healing of the destructive bone lesions with flattening of the acetabulum.

CASE 4: A girl, birth weight 2,211 grams, gestational age of 34 weeks (50th to 75th percentile I.U.G.C.), was born to a 20-year-old primigravida M-A woman. The mother had had no prenatal care and was admitted in active labor with vaginal bleeding. At delivery the infant was severely depressed, with an Apgar score of 2. On arrival at the nursery the infant was limp, cyanotic and gasping. The lungs were filled with crackling rales and thick mucus was suctioned from the trachea. The abdomen was greatly distended. The liver was palpated 9 cm below the right costal margin and the spleen 4 cm below the left costal margin. Radiographs of the chest showed bilateral diffuse pulmonary infiltrate and bone changes in the clavicles consistent with congenital syphilis. Results of Kolmer and VDRL tests on cord blood were positive (Table 1). Intravenous fluids and parenteral penicillin were started by one hour of age, but the infant died at five hours.

At post mortem examination,* enlargement of liver and spleen were noted. All the lobes of the lung were poorly aerated. Focal gumma formations were found in the lungs and the liver. The air spaces contained large numbers of fibroblasts and histiocytes. The portal triads of the liver showed fibrosis and acute cholangitis. There was extramedullary hematopoiesis in the lungs, liver, spleen, kidneys and adrenal glands. Fibrosis and extensive endarteritis were found in the pancreas, thymus, gastrointestinal tract, lungs and portal areas of the liver. Darkfield examination of the lungs was positive for Treponema pallidum.

CASE 5: A baby girl, birth weight 2,500 grams, gestational age 38 weeks (10th to 25th percentile I.U.G.C.), was born to a 30-year-old woman, gravida 7, para 5, ab 1. The mother had recently arrived from Mexico and had had no prenatal care. Pregnancy was normal and delivery uncomplicated. The infant was normal at birth, was discharged from the nursery in good condition before a report of positive results of tests for syphilis on the mother's blood, and was lost to follow-up.

At two and one-half months of age the baby was returned to the hospital out-patient department with complaint of rash on the palms. She was returned again the following week with a complaint of tenderness and decreased movement of the left leg. She was irritable, had purulent rhinorrhea with crusting around the nares, scaly vesicular rash of hands and feet and tenderness of the left leg. Long bone radiographs showed multiple destructive bone lesions consistent with congenital syphilis. Results of Kolmer and VDRL tests were positive (Table 1). Spinal fluid examination showed clear fluid with 5 lymphocytes per field, protein 127 mg per 100 ml and sugar 68 mg per 100 ml. The infant was admitted to hospital, treated with parenteral penicillin for two weeks and was discharged in good condition.

When seen one month later she was alert and active, with normal growth and development. Radiographs of long bones showed healing of lesions.

CASE 6: A boy, birth weight 3,320 grams, gestational age 38 weeks (75th percentile I.U.G.C.), was born to a primigravida who had come from Mexico eight months before delivery and had had no prenatal care. Pregnancy and delivery were uncomplicated. The infant was normal at birth and was discharged before the mother's serologic tests were reported positive for syphilis. The infant

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was referred for evaluation to the hospital clinic at two weeks of age. He was alert, active and well nourished. The skin in the inguinal area was reddened but not macerated. Radiographs of the long bones were normal. Results of Kolmer and VDRL tests were positive. The baby was returned to the clinic at three weeks of age, and Kolmer and VDRL tests done then were reported as negative. He was discharged from the clinic without treatment at one month of age.

At two and one-half months of age he was admitted to the hospital with redness and limitation of movement of the right upper arm. He had been well until, two days before admission, the mother "pulled his arm" when bathing him. On admission he appeared alert and well nourished. The spleen was palpated 3 cm below the left costal margin. Radiographs of the long bones showed multiple destructive lesions consistent with congenital syphilis. Kolmer and VDRL tests were positive (Table 1). After treatment with parenteral penicillin for two weeks the baby was discharged in good condition.

When last seen, at four and one-half months of age, he was alert, active and developing normally.

Discussion

The clinical features of congenital syphilis are related to the time of onset of symptoms. The classically described triad of pseudoparalysis, rhinitis and maculo-papular rash which alerts the physician to the clinical diagnosis has not been present in the nursery in our patients. Rather, the infants who were ill from birth presented with non-specific signs and symptoms which are associated with transplacental infection of various kinds. Consequently, the clinical diagnosis was more difficult in the early cases, and yet prompt recognition of congenital syphilis is particularly important, as it is one of the few transplacental infections for which effective treatment is available. Infants who were sick in the nursery had signs and symptoms present at birth, and all were severely ill. The disease was most severe in the premature infants.

Syphilis has been the most frequent transplacental infection encountered in our nurseries in the last four years. In descending order are rubella, herpes virus hominus, and cytomegalic inclusion disease. Toxoplasmosis has occurred rarely. The typical bone lesions seen in congenital syphilis have been the greatest aid to early diagnosis. Except for the bone lesions, none of the clinical manifestations in the cases presented are limited to congenital syphilis.

According to previous reports, in the nursery congenital syphilis presents most often as a hemolytic disorder with anemia, jaundice and hepatosplenomegaly or as a bleeding disorder with thrombocytopenia.[5,6] Three of our four patients had splenomegaly, two had hepatomegaly and evidence of hemolytic anemia. The hemolytic anemia is clinically indistinguishable from that caused by other transplacental infections or hemolytic disease secondary to blood group incompatibility and is characterized by anemia, reticulocytosis and distortion of red blood cell morphology. Previous reports have emphasized the presence of jaundice which may be so severe as to require exchange transfusion.[5] The bilirubin often has a high direct component and is associated with abnormal liver function. Jaundice was not prominent in the infants presented. Only one of them had jaundice and it was minimal and not prolonged, but it was clearly differentiated from physiologic jaundice by the high direct component and the accompanying hepatomegaly.

The frequency of respiratory distress and radiographic signs of interstitial pneumonia in the infants with neonatal disease was an unexpected finding. Respiratory distress was the most common symptom, the most troublesome in management, and the direct cause of death in the one infant who died.

Transient nonspecific neurologic findings occurred in the four patients with clinical disease in the nursery. All were considered to have poor muscle tone. Two of the four infants had decreased movement of an extremity—in one case probably related to delivery rather than infection. In the one case in which spinal fluid examination was done in the nursery, there was elevation of the protein content. Although the neurologic findings were transient, spinal fluid examination should have been performed in all cases of congenital syphilis, for such information is necessary in evaluating any future neurologic difficulty.

Generalized lymph node enlargement has been reported to be a frequent and characteristic finding in congenital syphilis.[3] Lymphadenopathy was not prominent in the infants presented. Only one infant had axillary adenopathy, and it minimal.

One of the most consistent clinical findings of transplacental infection is intrauterine growth failure. Congenital syphilis has long been known to be associated with prematurity by weight.[7] Two

of the four under-sized infants presented here were truly premature, with gestational age of 34 and 35 weeks. They were the most severely affected. None of the infants showed significant growth failure as judged by Denver Intrauterine Growth Curve,[4] although the two who were born at term had clinical evidence of intrauterine malnutrition in the peeling skin, decreased subcutaneous tissue, and meconium staining.

In summary, the infants with clinical disease in the nursery did not present with the "classical" triad of congenital syphilis but had the generalized nonspecific findings of transplacental infection described above.

In contrast, the remaining two infants, who appeared normal in the nursery, later developed the "classical" signs of congenital syphilis—rhinorrhea, rash and pseudoparalysis. Rhinorrhea is reported to be present in half of the cases of congenital syphilis.[7] It begins as a benign appearing mucoid discharge and rapidly progresses to an unrelenting sero-sanguinous exudate. The rash of congenital syphilis is characteristically described as being scaly-vesicular with prediliction for the hands and feet, particularly the palms and soles. Reddened macerated "diaper rash" is also commonly found, occurring primarily over the anal and buttock area and proving to be resistant to conventional treatment. The third entity of the triad, pseudoparalysis, is seldom found in an infant except in congenital syphilis.[7] In addition to the triad of congenital syphilis, the nonspecific symptoms of irritability, anemia and failure to thrive, with secondary infection, emphasize the generalized nature of the disease.

In all the cases presented herein there was radiographic evidence of bone disease.[8] This was the only constant finding in both the infants who were ill in the nursery and those who became ill later. This finding coincided with clinical symptoms: the bone radiographs were normal in an asymptomatic infant and showed disease when the infant became ill (Case 6). The radiographic changes remained after the patients were clinically well. Healing was slow, and bony changes were evident up to two months after evidence of active disease had disappeared.

Serologic diagnosis of congenital syphilis can be misleading unless several factors are considered. The infant's cord blood mirrors the mother's to a large extent. Positive results of serologic tests in the newborn do not mean disease is present;[9] it may reflect a biologically false positive maternal reaction or inactive maternal disease. The infant's serologic tests may be falsely negative if the maternal infection has been recent. Several recent articles have reviewed methods of serologic diagnosis of syphilis.[9,10,11]

Invasion of Treponema pallidum produces antibodies of two basic types: (1) antibodies known as reagins, which are not specific to the treponema organism, and (2) antibodies to the treponema organism itself. The non-treponemal antigens produce two varieties of antibodies: univalent antibodies (Kolmer and Wasserman), detected by complement fixation tests and bivalent antibodies (VDRL and Kahn) detected by flocculation test (Table 3). Either test may be reported quantitatively or qualitatively. The univalent complement fixation antibody passes through the placenta but the bivalent flocculation antibody *may* not.[9] This would account for the differences of reaction between mother and newborn with various tests. Since the half-life of passively transferred reagin is approximately 32 days, at one month of age, a 50 percent reduction in quantitative titers or reagin antibody occurs. The infant's blood titer should return to normal within three months if the positive reaction is due to passively transferred reagin and no intrauterine infection has occurred. In Case 6, in which the Kolmer was reported as positive at two weeks and negative at three weeks, a laboratory error should have been suspected and the test repeated before the infant was discharged to follow-up. These tests are obviously not specific for syphilitic infection in the immediate newborn period, although they have the advantage of being practical and widely available.

The specific treponemal antigen tests are Tre-

TABLE 3.—*Sero-Diagnosis of Congenital Syphilis*

I. *Non Treponemal Antigen Tests*
 A. Flocculation Tests (monovalent antibodies)
 VDRL
 Kahn
 B. Complement Fixation Tests (bivalent antibodies)
 Kolmer
 Wasserman

II. *Specific Treponemal Antigen Tests*
 A. Treponema Pallidum Immobilization (TPI)
 B. Flourescent Treponema Antibody (FTA)

III. *Serum Immuno-Globulin*
 A. Non-Specific
 Immuno-Globulin M (γM)
 B. Specific Treponemal
 γM Fluorescent Treponemal Antibody Absorption (γM-FTA-ABS)

ponema pallidum immobilization test (TPI)[12] and fluorescent treponemal antibody absorption test (FTA-ABS).[13] The TPI antibody develops more slowly than non-treponemal antibodies, and the TPI test is less sensitive in early syphilis. The FTA-ABS test is more specific and more sensitive than the TPI.[13] Since these antibodies do cross the placenta these are tests for maternal infection but are not specific for newborn infection.

The fetus has been shown capable of producing antibodies in response to intrauterine infection.[14] The antibodies produced *in utero* reside in the γM globulin fraction and since IgM does not cross the placenta, detectable levels at birth are believed to be the result of fetal production. Cases of intrauterine infection often have elevated levels of IgM in the cord serum.[15] In the present series, both clinically ill newborn infants in which IgM levels were obtained (Table 1) showed significant elevation. Elevation of IgM is not specific for congenital syphilis and has been found in other intrauterine infections such as toxoplasmosis, rubella and cytomegalovirus.[15] A specific FTA-ABS test using fluorescent-labelled antihuman IgM to demonstrate only syphilitic antibodies produced by the infant has been reported by Scotti and Logan[16] and by Alford et al.[17] This test was performed in four of the cases herein reported (Table 1) and was positive in all.

Treatment for congenital syphilis is simple and effective. Procaine penicillin G in aqueous suspension, 150,000 to 200,000 units per kilogram of body weight divided into ten equal daily intramuscular injections is our recommended therapy. The relapse rate is reported to be 5 percent.[18] Kanamycin and ampicillin, although effective in the management of one of the patients in the present series, are not the drugs of choice for therapy of congenital syphilis.

Although the infants may be desperately ill and die in the nursery, all the surviving infants in this series did well after discharge from the hospital. On follow-up all babies were growing normally and were alert without evidence of neurologic sequelae. Hemoglobin levels returned to normal rapidly although hepatosplenomegaly persisted up to two months after treatment. Despite treatment, interstitial keratitis, neural deafness and Clutton's joints may develop years later,[6] and for this reason prolonged follow-up of all cases is important.

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Primary Malignant Tumors of the Heart

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Because of their rarity, primary malignant tumors of the heart continue to evade clinical preoperative diagnosis. In five cases of malignant heart tumor that were reviewed from the diagnostic point of view, the clinical symptoms and radiographic abnormalities were found to be similar to those produced by more common heart diseases. The diagnosis of malignant cardiac tumor should be considered in a patient with heart disease who has (1) an unusual cardiomediastinal silhouette, (2) an atypical cardiac calcification, and (3) clinical or radiographic cardipulmonary findings which do not conform to the expected behavior of the common forms of heart disease.

PRIMARY MALIGNANT NEOPLASMS of the heart are rare.[1] The clinical and radiographic patterns are various depending upon the location of the lesions within the heart and their tendency to metastasize. The subject, although previously reported by others,[2-8] has received rather little emphasis in the literature[9] because of the rarity of the lesions.

The purpose of this report is to present our experience in five cases of primary malignant cardiac tumors and to review the pertinent literature.

Reports of Cases

CASE 1. A 37-year-old Caucasian man consulted his family physician because of progressive exertional dyspnea of six months' duration. Physical examination revealed plethora of the face and neck, and distended veins in the neck and both arms. Immediate admission to hospital was advised, but the patient refused and was treated with diuretics and digitalis. A few months later he was admitted to hospital because of progression of symptoms. A roentgenogram of the chest at that time showed enlargement of the right atrium with an increased density, seen in the posteroanterior projection in this area (Figure 1). The pleura on the right contained a small amount of fluid. The

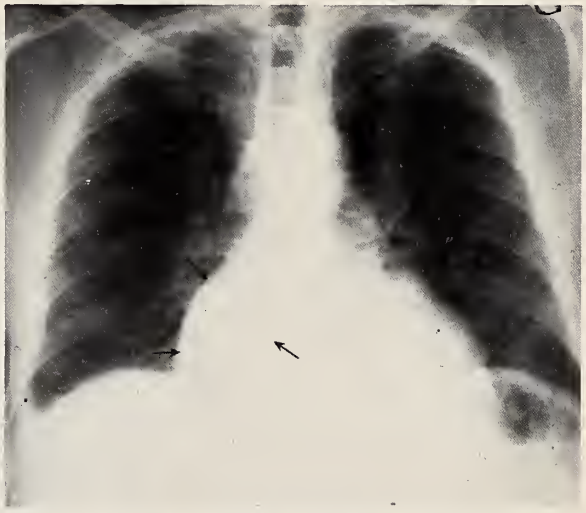


Figure 1. (Case 1.) Enlarged right atrium with increased density.

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Figure 2. (Case 1.) Ovoid densities projecting over anterior heart. Small amount of fluid in the right pleura with blunting of the posterior costophrenic angle.

lateral projection revealed two irregular, oval anterior densities in the region of the right atrium with a prominence in the superior right atrial region, possibly the right atrial appendage (Figure 2). On thoracotomy, a tumor of the right atrium was found. The patient was referred to the University of California, San Francisco (UCSF) for definitive surgical operation. On admission, facial plethora and edema were present. The veins of the neck and arms were distended, but not those of the legs. Cavography revealed complete obstruction of the superior vena cava. At operation, a large intramural tumor was seen to involve the wall of the right atrium; it completely occluded the superior vena cava and partially occluded the inferior vena cava. The tumor infiltrated into the right ventricular wall and through the pericardium into the hilus of the right lung. Palliative resection was done to restore blood flow into the right atrium. Histologic sections of the tumor showed angiosarcoma. Postoperatively, signs of obstruction of the superior vena cava resolved and the patient received a course of radiation therapy to the mediastinum. Five months after operation the patient was receiving chemotherapy because of metastatic pleural lesions, but further evidence of vena caval obstruction was not apparent.

Case 2. An 18-year-old Caucasian man consulted his school physician because of six weeks of progressive shortness of breath. After evaluation at another hospital, he was told that he had a heart murmur and pulmonary fibrosis. Two weeks later, progressive dyspnea, hemoptysis, edema of the legs, and mucoid sputum were noted. He was treated with digitalis, diuretics, and antibiotics, and then referred to UCSF for further evaluation. Previously, he had been healthy and had engaged in competitive sports.

On physical examination, the patient was pale and thin and appeared chronically ill. He was short of breath. Examination of the lungs revealed dullness and decreased breath sounds in both bases, but no rales. The pulmonic closure sound was accentuated and a moderate left parasternal dia-

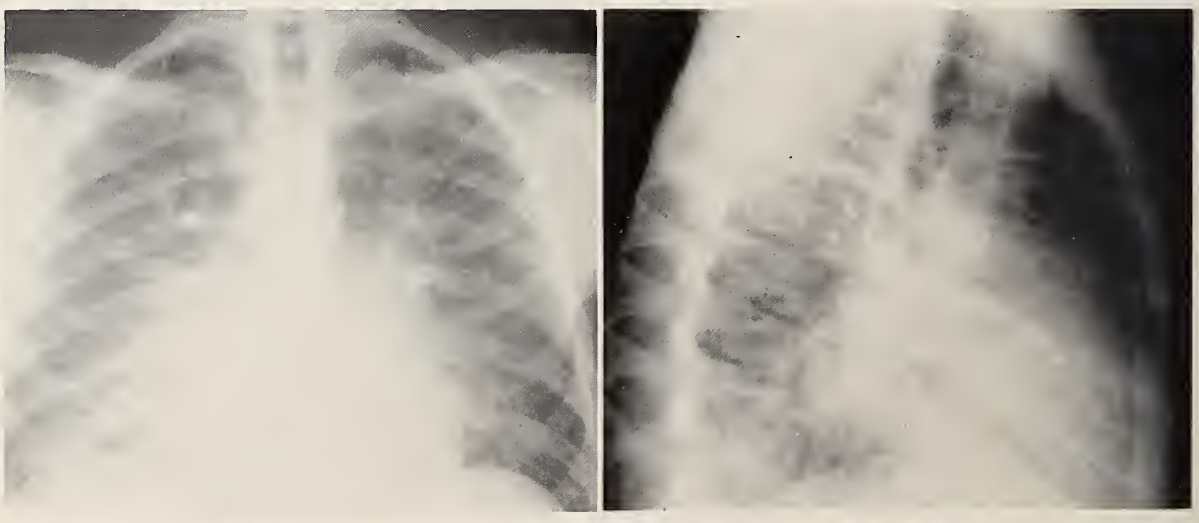


Figure 3. (Case 2.) Diffuse interstitial edema and left atrial enlargement.

stolic murmur and a holosystolic left parasternal murmur, which radiated to the apex, were heard. The sedimentation rate was 15 mm per hour. Changes in the electrocardiogram were "consistent with pulmonary heart disease." The initial chest film showed extensive interstitial pulmonary edema with left atrial enlargement and Kerley A and B lines (Figure 3). Cardiac fluoroscopy showed a mobile square calcification in the region of the mitral valve (Figure 4). It was situated in and above the valve and moved synchronously with the atrial contractions rather than with the valve excursions. A cineangiocardiogram showed that this calcification moved in association with an intracavitary left atrial mass. The catheterization revealed an increased arterial capillary wedge pressure with a 15 mm gradient over the mitral valve.

At thoracotomy a 3 × 4 cm large irregular, partly calcified tumor was found in the left atrium, which was adherent to the anterior leaflet and the annulus of the mitral valve, and invaded the left atrial myocardium. The tumor was resected partially to improve blood flow across the mitral valve. Histologic sections of the tumor showed a malignant mesenchymoma composed primarily of fibrous tissue with numerous mitoses and also of myxomatous, cartilaginous, and bone elements. An x-ray film of the chest on discharge from the hospital showed pronounced improvement of the interstitial pulmonary edema.

Case 3. A 59-year-old Caucasian man consulted his family physician because of progressive pain in the chest, abdomen and bones, of one year's duration. The patient had no symptoms of congestive heart failure or weight loss. Physical examination showed a normal appearing man in no acute distress. Discrete firm masses were palpated in both axillae, in the inguinal areas, and in the left supraclavicular and infraclavicular fossae. The heart, lungs, and abdomen were essentially normal. The sedimentation rate was 41 mm per hour. Roentgenograms of the chest showed a bulge along the left upper border of the heart, which was first thought to be a left ventricular aneurysm (Figure 5). The bulge was higher than would be expected for a ventricular aneurysm, however, and appeared to involve the left atrium as well (Figure 6). An electrocardiogram appeared normal. On fluoroscopy of the heart the contour was seen to pulsate paradoxically. A biopsy of the right supraclavicular lymph node showed matastatic undifferentated carcinoma. The course for the next two months deteriorated pro-



Figure 4. (Case 2.) Coarse square calcification in region of mitral valve (arrows), and horizontal left main bronchus indicating left atrial enlargement.

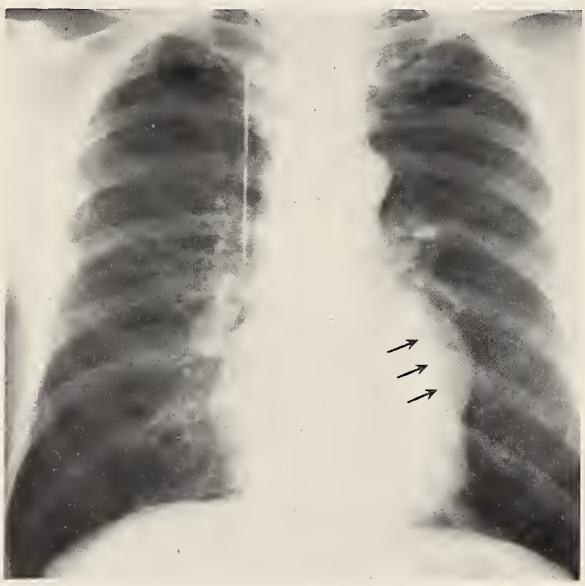


Figure 5. (Case 3.) Abnormal contour of left upper cardiac border, atypical location for left ventricular aneurysm. The linear density near the superior vena cava is an artefact.

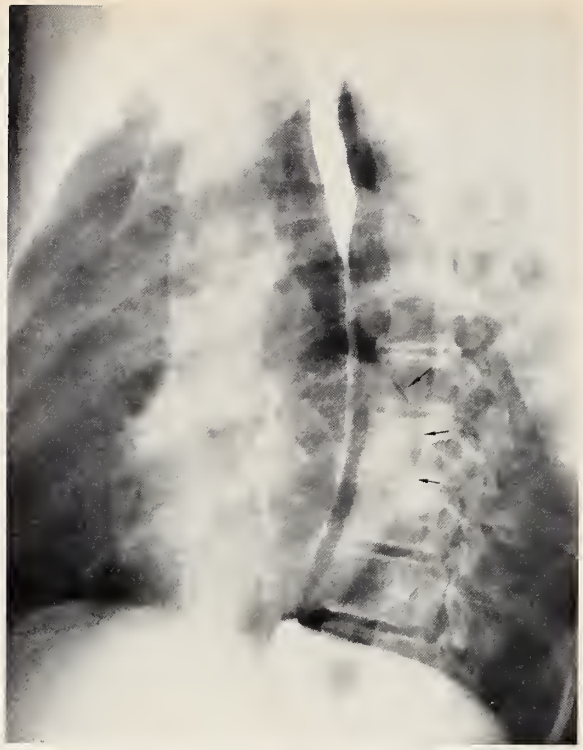


Figure 6. (Case 3.) Posterior upper abnormal contour, confirming atypical location for ventricular aneurysm.

gressively and was accompanied with extreme anterior right-side chest pain and epigastric pain, radiating to the spine. An exhaustive search for a pulmonary neoplasm was fruitless. The patient subsequently died and a postmortem examination at another institution revealed a rhabdomyosarcoma of the left atrium and left ventricle with diffuse distant metastasis.

Case 4. A 50-year-old Caucasian man sought medical attention from his physician because of cough and right anterior chest pain of several months' duration. A miniature film one month earlier was said to have been normal. Over the next two weeks, after treatment with antibiotics and physical therapy, the cough disappeared. The chest pain, however, became pleuritic in nature and was localized to the right mid-thoracic region. A film of the chest showed a somewhat globular, enlarged cardiac silhouette. Two months later the cardiac silhouette had considerably increased in size and had a more triangular configuration. Pericardiocentesis yielded a bloody effusion. Symptoms of tamponade required a second pericardiocentesis. The patient was transferred to UCSF for operation.

On admission, the patient appeared lethargic and complained of severe back pain. The neck

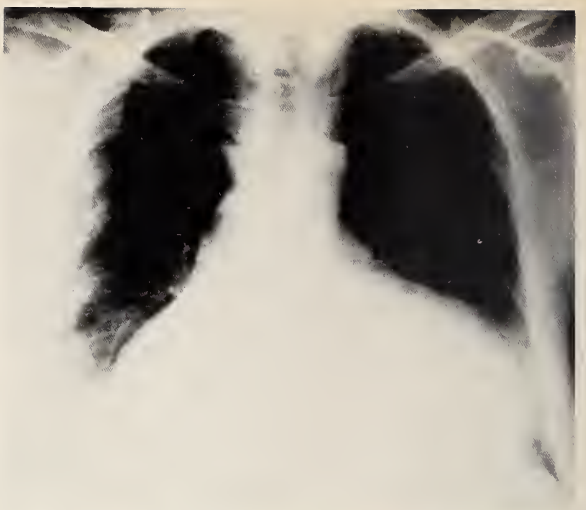


Figure 7. (Case 4.) Massive pericardial effusion suggested on admission film.

veins were flat and heart sounds distant. Sedimentation rate was 18 mm per hour. An electrocardiogram showed nonspecific ST and T wave changes consistent with pericardial effusion. A film of the chest showed right pleural effusion and massive cardiomegaly with a configuration compatible with pericardial effusion (Figure 7). A superior vena cavogram revealed a 65 mm distance from the outer aspect of the contrast medium to the outer aspect of the right cardiac border, presumably caused by a massive pericardial effusion. Pericardiocentesis and a pericardial exploration revealed 1,600 ml of blood in the pericardial sac. In the region of the right atrioventricular groove there was a soft nodular mass with blood oozing from its base. Histologic sections of the mass revealed angiosarcoma. The patient's postoperative condition became progressively worse and was marked by massive intraperitoneal bleeding and a series of cardiac arrhythmias, including final asystole. On necropsy, an angiosarcoma of the right atrium with metastatic growth in the lymph nodes, liver, spleen, and bone marrow was seen.

Case 5. A 17-year-old Caucasian boy was admitted to another hospital because of weakness, weight loss, and cough of several months' duration. The physical examination at that time revealed distended neck veins, a regular tachycardia at 140 beats per minute, pronounced accentuation of the pulmonic closure sound and a left parasternal systolic ejection murmur. Electrocardiogram showed changes compatible with "right atrial strain and inferior ischemia but no signs of right ventricular hypertrophy." Roentgenograms showed

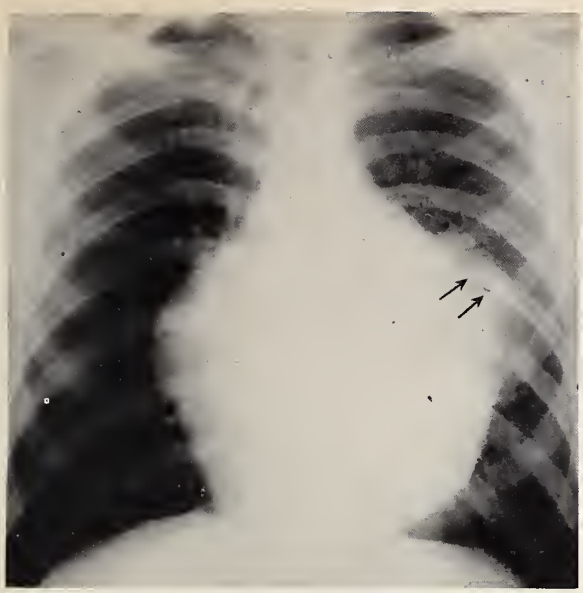


Figure 8. (Case 5.) Lobular polycylic contour to cardiac silhouette. Left pulmonary artery is displaced laterally (arrow).

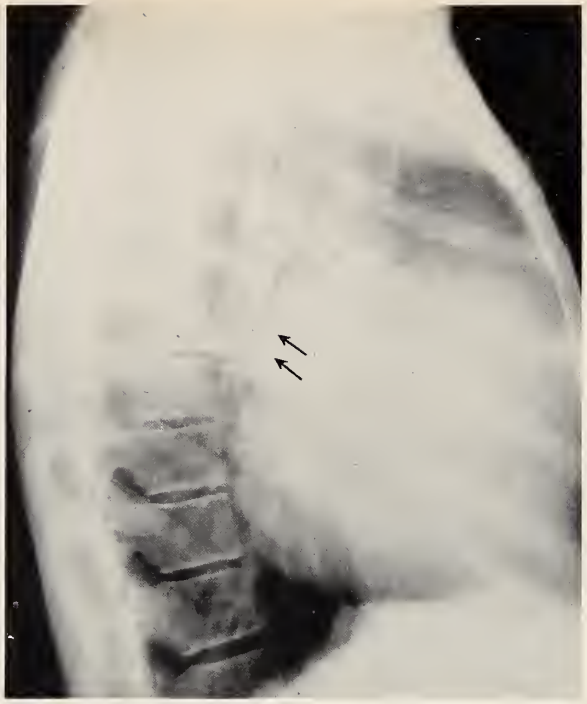


Figure 9. (Case 5.) Retrosternal space is filled in and there is associated narrowing of lower lobe bronchi (arrows). The heart appears posteriorly displaced.

irregular enlargement of the heart with polycyclic contour and filling in of the anterior mediastinum (Figures 8 and 9). The left lower bronchial lobe was compressed. The left pulmonary artery was pushed laterally and posteriorly. An angiocardiogram showed narrowing of the right ventricular outflow tract and the main pulmonary artery. The findings suggested either mediastinal tumor with cardiac involvement or primary cardiac tumor. The patient was referred to UCSF for further evaluation.

On admission the physical findings were essentially the same as those described above. Tomograms of the mediastinum revealed narrowing of both right and left main-stem bronchi. Subsequent fluoroscopy and angiocardiography revealed a large anterior mediastinal mass, which compressed the right ventricular outflow tract and the pulmonary artery. The interpretation at this time suggested mediastinal tumor with cardiac invasion. The sedimentation rate was 32 mm per hour. At operation a thick tumor beneath the epicardium enveloped the heart completely. It extended from the tip of the left ventricle around the great vessels and to the level of the right innominate vein. The tumor was 3 inches thick in the region of the right ventricular outflow tract. Sections revealed rhabdomyosarcoma or undifferentiated sarcoma. The patient was given 6,600 rad for 67 days with a 60-Co source. During the ensuing five months, progressive changes of pulmonary fibrosis developed. The patient died seven months after operation at another hospital of pulmonary insufficiency secondary to irradiation fibrosis.

Discussion

All primary malignant neoplasms of the heart are sarcomas.[10] They include angiosarcomas,[11] leiomyosarcomas,[12] rhabdomyosarcomas,[10] liposarcomas[13] and myxosarcomas. Malignant pericardial tumors have been reported.[14] It should be emphasized that secondary malignant tumors of the heart are about 20 to 40 times more common than primary neoplasms.[1] One common method of classification of primary cardiac tumors is by their location within the heart.[6] Histologic type bears no consistent relation to the site within the heart, except for angiosarcoma, which has a predilection for the right atrium.[11,15] Because of the subjective interpretation of the predominant cell-type in mixed tumors, and no universally accepted criteria for malignancy, detailed histologic classifications of malignant tumors are somewhat artificial.[16,17]

Far more important than the cell-type is the proximity of the tumor to vital intracardiac structures. Thus, a topographical classification allows a workable correlation with physiological aberra-

tions that produce clinical symptoms and roentgenographic changes. The invasive nature of some tumors results in involvement of more than one layer of the heart. Three different types of growth were found in our series:

Exophytic growth

Because of its location, any exophytic tumor may produce abnormal cardiac contours on roentgenograms. Our cases 1, 3, 4 and 5 are in this group. The large irregular, polycyclic cardiac contour and extension of mass into the anterior mediastinum in Case 5 suggests the diagnosis of mediastinal or cardiac tumor. Localized abnormal contours may be confused with more common entities, such as ventricular aneurysm, as in Case 3. On fluoroscopy the tumor may appear to pulsate paradoxically and change in contour with expiration and the Valsalva maneuver. Feist (1970) expressed the belief that cinefluorography without contrast material allows differentiation of ventricular aneurysm from solid masses. In a case of ventricular aneurysm he observed a time lag between the onset of systole and the often cyclic motion of the aneurysm. A solid tumor, in contrast, is characterized by rigidity or lack of cyclic deformity and by absence of a lag. The irregular cardiac contour in Case 1, with the ovoid densities projecting anteriorly over the region of the right atrium, suggests masses in this region. Tumors that extend to the pericardium may produce bloody effusions. Resulting tamponade, as in our Case 4, may be life-threatening and requires emergency operation.

Intramural growth

Intramural tumors may produce hemodynamic alterations by the production of conduction abnormalities and by preventing efficient myocardial contraction. Cardiac arrhythmias may result in cardiac failure. The patient in Case 4 died of progressively severe arrhythmias. An intramural tumor may be difficult to differentiate from cardiomyopathies that appear as diffuse or localized muscular masses, as for instance in hypertrophic myocardiopathy.

Intracavitary growth

Tumors with intracavitary extension may produce morbidity by obstruction to blood flow, mechanical hemolysis,[18] or embolization of thrombi or tumor cells.[4,19] In Case 2, the symptoms were clinically attributed to mitral stenosis. The evidence of severe interstitial pulmonary edema on the plain films and the data obtained on cardiac catheterization supported this diagnosis. At cineangiocardiography the unusual nature of the cardiac calcification was apparent. An intracavitary mass was demonstrated and a tumor was diagnosed preoperatively.

Sometimes a tumor, regardless of its location within the heart, never produces significant cardiac symptoms. In our Case 3, the patient's entire clinical course was dominated by bone pain that resulted from metastatic disease. Other frequent manifestations of malignant cardiac tumors include non-specific constitutional symptoms such as weakness, weight loss, and acceleration of the sedimentation rate,[2] which were present in most of our patients.

Roentgenographic Findings

Primary malignant cardiac tumors may produce abnormality detectable by chest roentgenograms, fluoroscopy, or angiocardiography. These findings depend upon alterations of the size or shape of the cardiomediastinal silhouette, presence of tumor calcifications, intracavitary masses, or secondary effects on extracardiac, intrathoracic structures. In four of our cases (1, 3, 4, and 5) there was abnormal cardiac configuration, the result of either pericardial effusion, exophytic growth from the heart, or mediastinal extension. In our second case, striking secondary pulmonary effects were related to obstruction at the level of the mitral valve.

Fluoroscopic findings included abnormal pulsations (Case 3) and the detection of calcifications (Case 2). Recording of the image on cineradiographs allowed a detailed study later of the calcified structures. The fact that location and motion patterns were inconsistent with mitral valve disease suggested the correct diagnosis of tumor. In one case (Case 5), angiocardiography showed extrinsic compression of the right ventricular outflow tract, but whether the mass was of cardiac or mediastinal origin could not be determined preoperatively.

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DECOMPRESSION SICKNESS*

WHY DO CIVILIANS, involved in sport SCUBA (self-contained underwater breathing apparatus) diving, appear to have a higher incidence of permanent damage following decompression accidents than do Navy divers? In a recent report from the University of Rhode Island (SCUBA Safety Report No. 3—"Nonfatal Pressure Related SCUBA Accidents"), statistics indicate that in a comparison of decompression accidents of civilians and U.S. Navy divers, the civilian sport divers had a 30 percent incidence of permanent damage following recompression therapy while for Navy divers the incidence was only 5.3 percent. Although the evidence is far from conclusive, it appears that the treatment of civilian divers is significantly less successful than it is for Navy divers.

The misinformation and general lack of understanding of decompression sickness by the sport diving public accounts for a large part of the delay in the diagnosis and treatment of this problem. One of the key factors in the successful treatment of decompression sickness is the time between the onset of symptoms and the initiation of treatment. Therefore, prompt diagnosis and immediate recompression are of paramount importance. However, confusion as to proper therapy, signs and symptoms, and the location of facilities capable of administering recompression therapy also has been responsible for serious time delays.

Signs, symptoms and complications of decompression sickness

Central Nervous System	*Cardiorespiratory*	*Extremities*	*Skin-Systemic*
Unconsciousness	Substernal pain	Pain	Rash
Spastic paralysis	Paroxysmal coughing	Numbness	Pruritus
Visual field defects	Tachypnea	Paresthesia	Pallor; low
Vertigo	Dyspnea (chokes)	Weakness	temperature; fever
Sensory loss	Shock	Aseptic Bone Necrosis	Fatigue
Bladder and bowel paralysis	Hemoconcentration	Joint destruction	All of the above

The accompanying chart is a brief compilation of possible manifestations of decompression sickness. Whenever cutaneous, cardiorespiratory and central nervous system symptoms are associated with a history of recent SCUBA diving activities, the possibility of a decompression accident should be suspected. Recompression is the therapy of choice and only a few specialized centers can offer you the proper facilities and personnel. Because of the expense of maintenance and operation, recompression facilities are almost exclusively run by the government. You may receive assistance and information by telephoning one of the following numbers:

Area	*Telephone Number*	*Area*	*Telephone Number*
Los Angeles/Long Beach	(213) 421-4741† or 590-2311†	Santa Barbara	(805) 966-3093†
		Monterey	(408) 375-2278†
San Diego	(714) 957-4439† or 295-3121†	San Francisco	(415) 986-5500†
		Bodega Bay	(707) 875-3596†

*Prepared by the California Medical Association Committee on Medical Aspects of Sports and Physical Fitness.

†U.S. Coast Guard Search and Rescue Operations' telephone numbers. The Coast Guard can provide transportation by helicopter or boat, supply information as to the nearest available recompression chamber, and put you in contact with a physician certified in submarine medicine to advise you in emergency situations.

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Left Atrial Myxoma

Diagnostic and Surgical Aspects

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Left atrial myxomas may present with signs of mitral valve obstruction, embolic phenomena or systemic disease. The diagnosis is suspected on clinical grounds and confirmed by angiocardiography. However, the tumor may be unexpectedly discovered on surgical exploration.

Once the diagnosis is established, operation, using cardiopulmonary bypass, should be done promptly. A coexisting valvular lesion should be looked for. Complete cure may be expected, especially if the involved atrial septum is excised and repaired by patch replacement.

LEFT ATRIAL MYXOMA presents a fascinating problem because of its rarity, protean manifestations and curability. The incidence is 0.27 percent in patients with a diagnosis of mitral valve disease.[1] Symptoms may be related to the hemodynamic effects of obstruction, to embolic phenomena or to systemic manifestations which may mimic collagen disease. Except for three cases[2-4] all successful removals of left atrial myxomas have been performed either with extracorporeal circulation or hypothermia. The first successful operation for left atrial myxoma using extracorporeal circulation was performed by Crafoord[5] in 1954 and using hypothermia by Bigelow[6] in 1955. Since that time there have been 87 additional successful cases reported.[7]

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Occurrence

Tumors of the heart are more likely to be metastatic than primary. In a review of 8,500 autopsies at the Mayo Clinic, Lymburner[8] found 52 cases of metastatic tumors involving the heart (0.6 percent) and only four primary tumors (0.05 percent). Myxoma is the most common primary intra-cavitary neoplasm of the heart and constitutes more than 50 percent of all primary cardiac tumors. Successful removal of myxomas has been

accomplished from all four chambers of the heart.[9-11] With a few exceptions cardiac myxomas arising in the left atrium are attached by a pedicle to the intra-atrial septum in the region of the fossa ovalis. Cardiac myxomas occur most frequently in the third to sixth decades[12] although they have been reported in patients aged three months to 85 years,[3,13,14] and are often reported to be more common in females.[3]

Pathology

The exact nature of atrial myxomas is disputed. Some investigators feel that they are atrial thrombi in various stages of organization while others view them as true neoplasms.[15,16] The latter view finds considerable support in the gross and microscopic appearance of the tumor, the systemic symptoms due to the tumor, the recurrence and the actual tissue invasion.[16] On electron microscopy, typical myxomas do not show the characteristic structure of a thrombus.[17]

Clinical Features

The clinical features of left atrial myxomas are related to hemodynamic obstruction, embolic phenomena or systemic manifestations. MacGregor and Cullen[18] in 1959 were the first to report systemic manifestations of fever, weight loss, anemia, increased sedimentation rate and elevated globulins with a left atrial myxoma. These findings are completely reversible after removal of the tumor.[19] The elevated gamma globulins suggest antibody formation perhaps due to myxomatous emboli, but what causes the systemic symptoms is unknown.[18]

The hemodynamic manifestations mimic mitral valve disease although the history may be of short duration. Symptoms may change dramatically over brief periods but may be present for periods of more than 12 years.[7] Once congestive failure occurs, it tends to be progressive and does not respond satisfactorily to medical treatment.[20] Variation in murmurs or symptoms with position or time is almost diagnostic.[7] When postural syncope occurs with other symptoms of mitral obstruction, a tumor should be suspected, for this symptom is rare in mitral stenosis.[7,21]

Systemic embolization occurs in about one-third of cases. It may be an early manifestation and may occur before obstructive symptoms.[20] In one series of five cases[7] embolic phenomena had been present in all cases and in one case the embolic episodes were present for 19 years before the onset of obstructive symptoms. Peripheral embolectomy of myxomatous tissue in six cases reported in the literature[2,22,23] resulted in the correct diagnosis, with subsequent excision of a left atrial myxoma in four of them. Embolic episodes in young patients or in older patients with normal sinus rhythm should arouse suspicion of this tumor. Myocardial infarction has been reported from tumor embolization, and neurological syndromes such as idiopathic epilepsy may be mistakenly diagnosed with this lesion. Arteritis has been mistakenly diagnosed with peripheral myxomatous embolization in a patient in normal sinus rhythm. During cardiac catheterization embolization may occur and left heart catheterization should be avoided. The actual surgical procedure also may be associated with embolization.[7]

The chest roentgenogram often closely resembles that of mitral valve disease. Kerley's B lines have been reported,[24,25] as has calcification of the myxoma, which has been confused with calcification of the mitral valve.[7] Phonocardiography may be helpful in offering clues to the presence of a mobile atrial tumor.[26] Heart scan and echocardiography are helpful non-invasive techniques in making the diagnosis.[26]

The electrocardiogram is non-specific in left atrial myxoma and only reflects the anatomical changes secondary to the tumor. Atrial fibrillation is present in only 14 percent of patients.[21]

Angiocardiography is certainly the most important diagnostic study. Pseudo-tumors are more common and varied on the right side of the heart;[28] however, a filling defect in the left atrium does not permit differentiation from a thrombus. Malm[29] cited two cases in which operation was performed for false filling defects in the left atrium. Often the angiogram is not only diagnostic but also spectacular; recently at the Surgical Spectaculars of the American College of Surgeons a pedunculated left atrial myxoma was shown bouncing in and out of the left ventricle through the mitral valve.[30]

Surgical Therapy

Once the diagnosis of left atrial myxoma has been made, operation should be done as soon as possible. An 8 percent mortality has been reported in patients awaiting operation following definitive diagnosis.[23] Firor, in 1966,[20] reported a patient in whom an atrial myxoma was found during digital commissurotomy for mitral stenosis; it was elected to proceed with the commissurotomy and

remove the myxoma under direct vision at a later date. Thirty-six hours after operation the patient died suddenly and at autopsy the tumor was found impacted in the mitral orifice. The group from Leeds[7] reported a similar problem in a patient operated upon in 1958. When they encountered the problem again in 1969, without readily available emergency bypass, they removed the tumor successfully under hypothermia at the same operation. Although there have been three successful removals of left atrial myxomas[2-4] without cardiopulmonary bypass or hypothermia, heart-lung bypass is the method of choice. There have been 15 successful operations for left atrial myxoma in 20 attempted cases using surface hypothermia and 46 successful removals in 49 attempted cases using cardiopulmonary bypass.[12]

A search always must be made for associated lesions. Bilateral atrial myxomas do exist and have been operated upon successfully.[31,33,34] Inspection of the mitral valve and its annulus must be made for possible significant changes secondary to trauma from the tumor. The possibility of associated mitral stenosis must be kept in mind.[7]

In almost all cases of left atrial myxoma the tumor is attached by a pedicle to the interatrial septum in the region of the fossa ovalis. Bahl[35] reported recurrence of a left atrial myxoma six years after it had been excised by cutting across the stalk, Gerbode[36] reported a recurrence four years after removal despite cauterization at the base of the excised lesion, and Walton[37] recently reported fatal recurrence two years following excision of the stalk with a cuff of atrial septum. Wide excision of the involved area of the interatrial septum and closure of the defect with a patch may safeguard against recurrence.

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Childhood Autism

A Review of the Clinical and Experimental Literature

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This review of the literature on childhood autism discusses the clinical characteristics, differential diagnosis, prognosis and treatment of the autistic behavioral syndrome from a developmental perspective. It includes a discussion of the influence of prenatal and perinatal antecedents, genetic and socio-familial factors, and epidemiologic considerations. Neurologic, electroencephalographic and experimental neurophysiologic, metabolic, biochemical and hematologic investigations are reviewed. Special emphasis has been given to the changing clinical manifestations which accompany maturation and to the problems of recognition of childhood autism in the very young child.

Of the many types of unusual behavior seen in young children, the behavior of the autistic child has been the most difficult to understand. The great variability of the abnormal behavior, the changes concomitant with the maturation of the child,[1,2] the wide differences in degree of severity from case to case, the confusing and inconsistent terminology which has been used to describe such children, and the lack of any physical signs have made diagnosis in the individual case a difficult and often unreliable procedure. The behavior is often so bewildering to the parents that it is hard to obtain an adequate description of the child's development. Often the parent can only say, "He is just different from other children"; unless the physician suspects the diagnosis and knows which symptoms to elicit, the diagnostic process may be thwarted at the outset and the physician may find himself saying, "Let's wait and see if he grows out of it."

Parental concern about the child's behavior may be communicated at any time. A mother may comment to her pediatrician that her newborn or month-old infant reacts very differently than her other babies. Neglected cases may not come to medical attention until the patient is as much as six or seven years of age. Parents usually seek professional help when the child is about two years of age since a delay in speech development is most likely to alarm parents at that time. Earlier and more subtle symptoms may have been ignored or denied.

What is the typical clinical appearance of the two- to four-year-old autistic child? The presenting problem may be delayed speech, and hearing

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loss may be suspected. In fact, many such children are first seen in speech and hearing clinics before the diagnosis of childhood autism is considered. On questioning, it may be found that although the child uses no speech or has ceased to use a few previously acquired words and does not respond to verbal commands, he does attend to certain sounds. In fact, he may seem to seek out auditory stimulation. For example, he may flick, rub or bang his ears, inducing quite intense auditory input, or he may scratch surfaces and put his ear to the surface listening to the sound that he makes. He may occasionally startle to quiet sounds or cup his hands over his ears and become agitated upon hearing a siren, a vacuum cleaner or perhaps just the distant sound of an airplane overhead. The child's failure to communicate with speech is often accompanied by a failure to communicate with gesture or pointing. The parents often complain that their child seems to look through them and that eye-to-eye contact is actively avoided. The child relates poorly to people in many other ways. He often ignores the presence both of other children and of adults. He may react to being picked up by struggling or becoming either completely limp or rigid. The child may show no interest in games or toys. He may wiggle his fingers, flap his hands, walk on his toes, rock, sway and whirl. This is the typical clinical appearance of a severely impaired two- to four-year-old autistic child. In less severe cases, or when seen at a younger or older age, only some of the symptoms may be present, the overall intensity of the symptoms may be milder, the bizarre behavior may occur more intermittently and the clinical picture will be less clear.

Terminology

At least six major diagnostic rubrics have been used to describe young children with this set of symptoms. Although isolated cases were reported earlier, the syndrome was first formally described in a group of 11 children by Kanner in 1943 under the heading "Autistic Disturbances of Affective Contact."[3] In 1944 Kanner adopted the term *early infantile autism,* drawing attention to the fact that the autistic behavior develops in early infancy.[4] This term and its synonyms—*childhood autism, infantile autism* and *autistic child*—have become the most commonly accepted way of referring to this condition. It is also occasionally referred to as Kanner's syndrome. A second diagnostic rubric is *atypical development.*[5-8] This term has been used to describe patients whose symptoms may be less severe. The term *symbiotic psychosis* has been used to describe children whose way of relating appeared superficially to be the opposite of an autistic way of relating.[9,10] The children, rather than being aloof and remote, would cling tenaciously to the parent. Since such behavior can be found transiently or intermittently in autistic children who are otherwise completely emotionally detached, this term does not describe an independent disorder.

The term *pseudo-retarded* or *pseudo-defective*[11] was used at a time when considerable emphasis was placed on the differential diagnosis between mental retardation and childhood autism. Many of the autistic children functioned at a retarded level, failed to relate to normal task-oriented social situations, and failed to use language. It was thought that the retardation was only apparent—an artifact of their untestability and inability to communicate.[11,12] Since more recent studies have demonstrated that the majority of autistic children are in fact permanently retarded, this term is no longer applicable.[13,14] The more general but less well defined term *infantile psychosis* and its synonyms —*childhood psychosis* and *early onset psychosis* —have been used extensively.[8,13-22] When used to describe children whose symptoms begin before 36 months of age, these terms are acceptable synonyms for childhood autism.

A final term which has received wide usage as a diagnostic label for this same group of children is *childhood schizophrenia.*[1,11,12,23-30] The use of this term has created some semantic confusion and much diagnostic controversy in the literature concerned with autistic children, since many students of this illness feel that childhood autism is phenomenologically quite distinct from the schizophrenias of later life[18,20,21,31] while others describe a continuum of symptoms relating the two syndromes.[11,17,32,33] Both the distinctions and the relationships between childhood autism and schizophrenia will be discussed in appropriate sections of this paper. The terms *childhood schizophrenia* and *schizophrenic child* will be used in this review as acceptable synonyms for childhood autism with the understanding that the patients have the set of symptoms described in the following sections and that the illness is recognized at less than five years of age and deviant development is present before three years of age. Children who definitely were free of autistic symptoms before they were five years old and then began to have schizo-

phrenic symptoms are not to be classified as autistic on phenomenologic grounds even though the underlying pathophysiologic mechanisms *might* be similar in the two groups of children.[34,35] The children who first became schizophrenic in middle childhood after a normal early development should not be called autistic and their disorder has been referred to as late onset psychosis.[18]

Clinical Course

Childhood autism begins at birth or early in post-natal life although in many cases the first symptoms may not be recalled or recognized by the parents. Two courses of development of the illness have been reported. In the first, the parents describe deviant behavior from birth. In the second, there seems to be a period of relatively normal development up to the age of 18 to 24 months, at which time the onset of symptoms occurs. The onset of the disorder will almost invariably occur before 30 months of age and rarely occurs past the third birthday.[18,20] The subsequent clinical picture is the same regardless of the exact age at onset of the first symptoms. Very careful history-taking may elicit symptoms which did indeed occur during the first year of life, but which were forgotten, overlooked or denied by the parents due to either anxiety about their child's development or unfamiliarity with normal development.

The neonatal period

The mother may be convinced that the newborn baby is different from her other babies but she cannot articulate the subtle nature of the strange behavior. The infant may cry infrequently or seem not to need companionship or stimulation. He may become limp or rigid when held. He is often described as a "very good baby" who never fusses, or as intensely irritable and over-reactive to any form of stimulation. Muscle tone may seem flaccid.[36]

The first half year

During the first half year of life the child may continue to be "undemanding" but it soon becomes apparent that he is failing to notice the coming and going of his mother. Responsive smiling does not occur or is delayed. At four or five months the normal anticipatory response to being picked up does not occur. Often a baby who is unresponsive to toys such as a bird mobile, rattle or a crib gym may be paradoxically over-reactive to sounds produced by the vacuum cleaner, the washing machine or the telephone. The earliest vocalization—cooing and babbling—may not appear or be considerably delayed.

The second half year

During the second six months, the baby often shows an unusual response to the introduction of solid foods. The usually uneventful introduction of strained baby foods is often followed by refusal to accept, retain, chew or swallow foods with rough texture such as chopped meats. Without intervention some autistic children remain on pureed baby foods for several years. Toys which were ignored in the first half year of life are now cast or flicked away or simply dropped out of hand. The motor milestones such as sitting, crawling, pulling to a stand and initiating walking occasionally are accelerated but are more likely to be delayed. Developmental sequences may be irregular; for example, late sitting without support may be followed by precocious pulling to a stand and then late walking.[1] If developmental testing is attempted at this time or during the second year of life these spurts and lags in development are often reflected in wide scatter on developmental profiles.[36]

The six- to twelve-month-old autistic baby is unaffectionate. When picked up he may become either limp or stiff, and when put down not seem to care. He often fails to show the normal eighth month "stranger anxiety" and does not play peek-a-boo and pat-a-cake at ten or eleven months of age.[37] At 12 months, he does not wave bye-bye responsively and syllables are not combined into polysyllabic sounds and words. Occasionally the child develops a few words and then a few months later ceases to use them. Along with the absence of communicative speech there is no nonverbal communication. The child neither points nor looks toward a desired object. Toward the end of the first year, peculiar reactions to sensory stimuli develop and continue into the third year of life. At times the autistic baby may become agitated or panicked by the same unexpected or loud sounds as those to which he is completely oblivious on other occasions. Changes in other sensory modalities—illumination, the feel of certain fabrics, and proprioceptive and vestibular sensations induced by change in position—may also evoke distress.

The second and third years

During the second and third years, the child seeks stimulation in all sensory modalities and

often engages in peculiar mannerisms which seem to provide such stimulation. For example, there may be noisy and vigorous tooth grinding or the child will scratch surfaces and listen intently to the sounds that he creates. He will place his eyes very close to the surface of an object such as a moving top and intently stare at the passing visual patterns. He will rub his hands over the surface of different fabrics, responding to fine textural differences. A number of unusual repetitive and stereotyped mannerisms involve the hands. The tendency of the normal six month old to intently regard his own hand and finger movements often becomes a permanent part of the autistic child's behavioral repertoire. He may either sustain this infantile mannerism or flap his hands or rapidly wiggle his fingers while regarding, often in the periphery of his visual field, his own hand movements. Other unusual motility patterns occur. The normal transient toe walking which accompanies the early stages of learning to walk may become a permanent behavior.[38] The children engage in excessive body rocking, swaying, and head banging[39] and often roll their head from side to side. They may whirl around and around for many minutes without becoming dizzy. In states of excitement all of these behaviors may be seen to occur together. Often in response to some stimulus, the child will suddenly run in circles on his toes, whirl, make staccato-like lunging and darting movements and vigorously flap his hands. The two- and three-year-old autistic child shows little or no interest in toys. Toy cars, dolls or puppets are ignored or arranged in some idiosyncratic pattern without regard to function or meaning. There is little or no development of imagination, fantasy or role-taking in play.[40] Preoccupation with spinning objects may preclude all other forms of play. A spinning top may elicit explosive yet organized bouts of motor discharge including toe walking, darting and lunging toward the top and a staccato flapping of the hands. The limited interest in toys is accompanied by indifference to human contact. The autistic child does not look at the adult when he wants something but moves the adult's hand toward the desired object much as if manipulating a pair of pliers.

The fourth and fifth year

Most of this behavior continues into the fourth and fifth year, after which the severe reactions to sensory stimuli and the bizarre motility patterns may abate. Then the focus of clinical attention may be the unusual speech. The child may remain mute or speech may be limited to a few inconsistently used words. When speech does occur, it is often limited to delayed echolalia. This is a parrot-like imitation of the speech of others occurring out of social context and having little or no communicative value. For example, the child might say, "Do you want to take a walk?" while bathing or eating, parroting word for word a question that was directed to him earlier in the day. Along with the echolalia there is misuse of the personal pronouns (the substitution of "you" or "he" for "I" or "me").

Middle childhood

After the fifth or sixth year, two types of progression of the disorder occur. Some of the children may continue to manifest most of the symptoms already described. In others, there may be a gradual change in the clinical picture; the symptoms of childhood autism become less evident and new features develop, suggesting either alternative or secondary diagnostic considerations (see section on prognosis below). With increasing age, the unusual responses to sensory stimulation and the bizzare motility patterns become less apparent. The disturbed relating is more likely to continue beyond the sixth year and its severity tends to be in proportion to its severity during the first five years. The same is true of the language disturbances, and if language has not been used consistently for communication by age five years, then it is extremely unlikely that more advanced speech development will ever occur. When this is the case, intellectual development remains at a standstill and if the extreme responses to sensory stimulation and the bizarre motility patterns abate, then the child begins to look less autistic and more and more retarded. This is not the case if the child develops communicative speech by his fifth birthday. In this case, one observes a child whose communications are very literal and who shows a reduced capacity for abstract thinking, a deficit which appropriate evaluation may be able to demonstrate in the younger nonverbal autistic child.[41] Affect tends to be flat, and verbal communication does not lead to emotional involvement with others. The child remains an aloof, emotionally detached and often bizarre-appearing youngster. In some cases the child's communications appear to be characterized by loose, irrelevant and tangential thinking, and if the child has developed any degree of fantasy life the expressed

fantasies tend to be bizarre and are often confused with reality. Another type of behavior seen in some autistic children between the ages of five and ten years is impulsivity and lack of emotional control, coupled with restlessness, irritability and hyperactivity.

The Behavioral Syndrome of Childhood Autism

The previous section of this paper has emphasized the developmental aspect of this disorder and the changes in symptoms with the age of the child. It is also helpful to think of several categories or subclusters of symptoms when making the diagnosis of childhood autism. These symptom subclusters include (1) disturbances of relating, (2) disturbances of speech and language, (3) disturbances of developmental rate, (4) disturbances of motility and (5) disturbances of perception.

Disturbances of relating

These symptoms involve relationships both with people and with inanimate objects. Behaviors indicative of an early failure to develop interpersonal relationships include poor or deviant eye contact,[42-44] delayed or absent social smile, delayed or absent anticipatory response to being picked up,[3,45] apparent aversion to physical contact, a tendency to react to another person's hand or foot rather than to the person,[45] disinterest in playing games with others and a general preference for being alone.[31,46] The disturbed interpersonal relationships may be more subtle and need not be consistently observed. Experiments carried out under well controlled laboratory conditions suggest that the disturbed relationships may not be fundamental to the disorder[47,48] but may be secondary to disturbances of perception.[49] The use of inanimate objects is limited to flicking, twirling or spinning them. There is a tendency to order and arrange objects in a constant manner so that the child seems to want to maintain an unvarying sameness in his environment.[3,40,45,50] With increasing age, these same tendencies are manifest in a rigidity and inflexibility in the use of play material.[51,52]

Disturbances of speech and language

Speech development is usually characterized by muteness or echolalia.[3,12,53-55] Along with the echolalia there may be misuse or reversal of the personal pronouns.[3,31,56,57] The tendency to echo the speech of others without regard for the social context or communicative value of the words may pervade tests of language function in autistic children. For example, while normal children always recall sentences better than non-sentences, autistic children remember "nonsense" as well as "sense"; their recall process seems to depend on an "echo box type" memory store.[47] Although attempts have been made to understand the echolalia of autistic children in a psychodynamic and psychoanalytic context,[56,58] the echolalia in autistic children probably is related to the severe rigidity of imitation observed in the speech of these children.[59] When communicative speech does develop it is atonal and arrhythmic, lacks inflection and fails to convey emotion.[29] This poverty of the tonal and affective qualities of speech in young autistic children is paralleled in older autistic children by a restriction of spontaneity and originality of communication.[52,60]

Disturbances of development rate

Autistic children show great irregularity in the age at which the sequential motor and language milestones are passed.[1,36] While some autistic children show either a normal or precocious developmental progression, a greater number manifest early developmental retardation. The most characteristic course, however, is to find discontinuities in the normal sequence of development.[61] For example, an autistic child may sit without support precociously, and then there may be a long delay before he will pull to a stand. Thus a sequence of spurts and lags is characteristic of the development of autistic children.[1] The unevenness of development is also manifest in the special abilities of some otherwise very retarded autistic children.[62]

Disturbances of motility

To a great extent the strange and bizarre appearance of autistic children is due to their peculiar mannerisms and motility patterns. The deviant motility may involve the hands, the lower extremities, or the trunk and entire body. While the mannerisms are often complex and ritualistic and clearly do not have the appearance of either involuntary movements or seizure discharge patterns, they are stereotyped, strikingly similar in general pattern and form in most autistic children, and do not seem to be entirely voluntary. The severity of this aspect of the syndrome varies decidedly from one autistic child to another. The deviant motility may appear intermittently or in-

frequently in some autistic children and may occur continuously in others.[63,64]

Some of the most characteristic and striking motor behaviors involve the hands.[2,63,65-68] The autistic child may hold his hands in front of his eyes and writhe or twist the fingers and palms. Activity of this type often merges into a repetitive stereotyped wiggling of the fingers or the entire hand. This "hand flapping" involves a rapid and untiring alternating flexion and extension of the fingers or hand or an alternating pronation and supination of the forearm. Similar "flapping" movements of the lower extremities may occur but the most striking involvement of the lower extremities is toe walking.[38] This may occur transiently during states of excitement or while running in circles. However, it is often the only mode of walking and may persist on occasion into adolescence.

Disturbances involving the trunk or the entire body include staccato lunging and darting movements, terminated by sudden stops. The children also engage in an unusual amount of body rocking and swaying, often accompanied by head rolling or head banging. A history of severe infantile head banging is often associated with the later development of self-mutilation.[39] The children also whirl themselves around the longitudinal body axis. In spite of all this gross motor activity, autistic children are not necessarily hyperactive. These children are not constantly in motion nor is there a restless, irritable quality to their activity. In fact, the various behaviors just described may be interrupted by sudden brief episodes of immobility, often associated with bizarre posturing of the trunk or extremities. Very young autistic children tend to arch the back and hyperextend the neck, maintaining this uncomfortable position for brief periods. Some or all of these motility patterns can at times be elicited by rapidly spinning a child's top in front of the patient.

Disturbances of perception

The disturbances of perception charactertistic of autistic children do not necessarily involve the perceptual deficits seen in children who have minimal cerebral dysfunction. These latter deficits involve difficulty in perceiving the shape of objects and their orientation in space, abilities which may be intact in autistic children. When such deficits do occur in autistic children, they may be secondary to a failure to sustain attention toward visual stimuli.[47] The disturbances of perception in autistic children involve a faulty modulation of sensory input,[2,34,69] a distortion of the normal hierarchy of receptor preferences,[70] and an impaired ability to use sensory input to make discriminations in the absence of feedback from motor responses.[47]

The inability to adequately modulate sensory input constitutes a striking aspect of autistic symptoms.[2,28,29,66,69] All sensory modalities are affected and the faulty modulation of sensory input may be manifest as either a lack of responsiveness or an exaggerated reaction to sensory stimuli.[28,29] Both types of abnormal reactivity to sensory stimuli can occur in the same child.[28]

Hypo-reactivity to auditory stimuli is apparent in the disregard of both verbal commands and loud sounds. Sudden sounds which would elicit an impressive startle reaction in normal children may elicit no response whatsoever in some autistic children.[71] Visually the children may ignore new persons or features in their environment and they may walk into objects as if they did not see them. A similar response to tactile stimuli may occur during the first two years of life; objects placed in the hand may be allowed to fall away as if they had no tactile representation. Painful stimuli are often ignored; the children may not notice painful bumps, bruises, cuts or injections.

Contrasting starkly to the hypo-reactivity to sensory stimuli are decidedly exaggerated reactions to the same stimuli. The children may show both heightened *awareness* of sensory stimuli and heightened *sensitivity* to sensory stimuli.[28] Along with the heightened awareness of sensation there is often a tendency to seek it out and induce it. Some of the disturbances of motility seem to provide intense sensory stimulation but may also be a way of mastering sensory stimuli.[72] The children tend to induce sounds by scratching surfaces and putting their ears down close to the surface. They may be distracted by background stimuli of marginal intensity. They may rub, bang or flick at their ears or grind their teeth—all activities that induce intense auditory input. Visually they regard their own writhing hand and finger movements or their more vigorous hand flapping, and they scrutinize the fine detail of surfaces. There are also brief episodes of intense staring. The children may rub surfaces of furniture or fabric in response to fine textural differences. Many of the behaviors of autistic children also suggest that they are actively seeking out vestibular and proprioceptive stimulation.[11,12] They whirl themselves around and

around, repetitively rock and sway back and forth, or roll their heads from side to side. The repetitive hand flapping also provides proprioceptive input.

Contrasting with both the tendency to ignore and to seek out sensory stimuli is the paradoxical distress induced by stimuli in all sensory modalities. The children may become agitated by the sound of sirens, vacuum cleaners, or barking dogs and they may cup their hands over their ears in an attempt to shut out both these intense sounds and also mild novel sounds such as the crinkle of paper.[28,69] Sudden changes in illumination or confrontation with an unexpected object may elicit the same fearful reactions to visual stimuli. In the tactile modality there may be severe intolerance for certain fabrics; the children are often disturbed by wool blankets or clothing and seem to prefer smooth surfaces. During the first year of life the introduction of the rough-textured table foods often evokes distress. The same child who may seek out vestibular stimulation by whirling himself can show a pronounced aversion to vestibular stimulation induced by roughhouse, anti-gravity play or even riding in an elevator.

Autistic children do not show the same preference in the use of the various sensory modalities as do normal or non-autistic mentally retarded children. They have been described as preferring to use "proximal" receptors (touch, smell and taste) rather than "distal" receptors (audition and vision).[70,73] Both autistic and non-autistic children tend to respond to light in preference to sound but non-autistic children can readily be conditioned to respond preferentially to a sound source whereas this is not possible with autistic children.[74] This apparent dominance of visual over auditory stimuli may actually be due to an inability to respond to two or more stimulus modalities in a complex stimulus presentation. Autistic children are overselective in responding to only one component of a stimulus complex consisting of, for example, auditory, visual and tactile components.[75,76] Visual stimulation itself seems less meaningful to autistic than to non-autistic children, in that autistic children show fewer eye movements in response to and spend less time regarding visual displays than do non-autistic children.[47,74] While autistic children may have normal or even advanced form perception[37] they make poor use of visual discrimination in learning.[74,77] They seem to be dependent on feedback from their own motor responses toward sensory stimuli in order to make sense out of perceptions.[47,78]

Differential Diagnosis

Childhood autism is not necessarily mutually exclusive with a number of conditions from which it must be differentiated. In particular childhood autism may coexist with mental retardation, a number of organic brain syndromes, and a variety of seizure disorders. The problem of differentiating childhood autism from these conditions with which it may also be associated will be returned to after considering other conditions where a more satisfactory differential diagnosis can be made.

Maternal deprivation

Since autistic children are described as having been "extremely good babies" who "prefer to be let alone" a lack of adequate stimulation during the early years is often considered in the genesis of the illness.[79] If the mothering of the infant has been characterized by aloofness, indifference and minimal physical contact, can this induce autistic behavior? Various degrees of environmental deprivation do indeed induce serious developmental disturbances in children. The immediate and long-term sequelae of environmental deprivation have been well documented both in infants raised in institutions[80,81,82] and in infants raised at home.[83] Environmental deprivation of young infants is to be understood to encompass at least three types of deprivation: (1) maternal deprivation involving deprivation of love, human contact, physical warmth and cuddling, and the give and take of social interaction with a caring adult; (2) an absence of novelty, resulting in an unrelieved condition of environmental monotony and boredom; and (3) an actual deficit of sensory input in all sensory modalities (auditory, visual, kinesthetic, tactile and vestibular). Infants reared in these circumstances show disturbances of developmental rate, motility, relating, language and perception. These are the same general aspects of development which are adversely affected in autistic children. The nature of the individual symptoms is quite different, however, in the environmentally deprived than in the autistic children.[66]

Environmentally deprived children suffer a uniform retardation of the acquisition of motor skills and speech as well as a delay in the adaptive use of toys. Autistic children show an uneven motor and speech development characterized by spurts and lags. Environmentally deprived infants show certain unusual motor patterns—for example,

athetoid movements of the hands. These movements do not develop into the tenacious, stereotyped hand flapping or finger wiggling of autistic children. Whirling, toe walking and darting and lunging movements of autistic children are not seen in environmentally deprived children. Environmentally deprived children do engage, however, in a considerable amount of body rocking and some hand posturing, but these activities are easier to interrupt than in autistic children. Like autistic children, environmentally deprived children show various disturbances of relating. They adapt poorly to holding but do not become limp or rigid as do autistic children. While the deprived children may flick at toys or drop them as do young autistic children, their general interest in toys remains undeveloped. Autistic children, in contrast, tend to use toys in bizarre ways, such as spinning them. Deprived children fail to seek adults out when given the opportunity, but unlike the autistic children, who seem to avoid eye contact, they engage in intense visual regarding of adults. While autistic children rarely develop active interest in playing games with others, the deprived children do participate in games although such interest develops later than in normals. When seen in the second or third year of life, children who have suffered from serious environmental deprivation may show a delay in language acquisition similar to that seen in autistic children. However, they do acquire language if the environmental deprivation is relieved, and once language is acquired the speech does not have the atonal, arrhythmic, hollow-sounding quality of the speech of autistic children, nor do echolalia and misuse of pronouns occur. The environmentally deprived children do not show the faulty modulation of sensory input seen in autistic children. In contrast to the tendency of autistic children to engage in excessive tactile exploration, the deprived children show a diminished tendency to touch themselves or to contact the environment through mouthing activity.

When the conditions of environmental deprivation are relieved, deprived children usually make significant gains. However, a number of sequelae have been observed. There is a persistent faulty self-regulation of food intake. The previously deprived children do not know when they are satiated, but they do not develop bizarre food preferences or exclude solid foods as do autistic children. There are residual mild deficits in coordination of body movement but the hand flapping and toe walking seen in autistic children do not occur. Residual lags in language development are not accompanied by the delayed echolalia of the autistic child. Instead of remaining emotionally detached from adults as do autistic children, the children recovering from environmental deprivation show an indiscriminate friendliness to them. They fail to develop strong emotional ties to any individual person. Again, on follow-up, environmentally deprived children do not show the sensory hypersensitivities and hyposensitivities or the preoccupation with spinning objects seen in autistic children.

When a mother has postpartum depression or other serious emotional disorder during her child's first year and adequate care of the child by a mother surrogate has not been provided, the physician should consider the following two possibilities. First, because of the mother's emotional state she may only be able to provide perfunctory care of her baby and the child may, in fact, develop the environmental deprivation syndrome due to maternal deprivation and the accompanying poverty of sensory stimulation. Second, the primary condition may be an insidiously developing autistic disturbance in the child which has an adverse emotional influence on a sensitive mother. The child's failure to relate to the mother and to respond positively to her ministrations may result in loss of self-esteem and a resultant maternal depression.

Anaclitic depression

Like the environmental deprivation syndrome, the anaclitic depression is accompanied by profound developmental retardation and severe disturbances of relating, and therefore it must be distinguished from childhood autism. Unlike the environmental deprivation syndrome, anaclitic depression is associated with the interruption after the sixth month of life of a good mother-infant relationship.[84] The interruption may be due to death, illness, depression or absence of the mother. The infant reacts by becoming weepy, demanding and clinging. If the mother does not return within a few weeks, this weepy stage progresses into a period of psychomotor and language retardation, weight loss and intense wailing. After two or three months, the child becomes lethargic and apathetic; the weeping and wailing are replaced by quiet whimpering, and facial rigidity suggests a profound depression. The motor and perceptual symptoms accompanying the syndrome of childhood autism do not occur and the failure to

relate to adults is characterized by apathy and withdrawal rather than the the lack of involvement characteristic of the autistic child.

Other behavioral disturbances due to environmental influences

In addition to the absence or loss of adequate mothering in the first and second year of life, various types of disturbances of the mother-infant relationship or disturbances within the family setting can induce unusual behavior accompanied by developmental lags in the child. Body rocking and some other unusual mannerisms, gestures and habits may develop during the first and second year of life in response to chronic frustration or traumatic emotional experiences. It is to be emphasized that not all *bizarre* behavior seen in young children implies childhood autism. In the differential diagnosis of childhood autism there must be a thorough assessment of family relationships and the mother-child relationship.

Since failure to use language is so prominent a part of the autistic syndrome during the first few years of life, the condition of elective mutism deserves special emphasis. In elective mutism the child is quite capable of the complete use of speech but voluntarily withholds it. These children have usually been heard to speak fluently at some time in the past or will speak fluently under certain limited conditions. For example, some electively mute children will only speak in the presence of other children and never when an adult is present. Others will only speak within, never outside the family. At times the child will speak only in a whisper. The voluntary withholding of speech is usually in response to a specific pathological family situation or mother-infant interaction. It occurs in response to premature attempts on the part of the parents to force speech development or in family settings where the need to keep a "family secret" has been unduly impressed upon the child.

Major sensory deficits

Deafness and blindness in early childhood can precipitate severe emotional reactions. The combination of such emotional disturbance with the limitations imposed by the sensory deficit can result in a clinical picture which may be confused with childhood autism.[85] Since absence or delay of speech acquisition almost always accompanies the syndrome of childhood autism during the first two years of life, hearing loss should always be considered. Adequate otologic examination to evaluate possible causes of chronic or intermittent hearing loss should be carried out. Some autistic children are first seen in speech and hearing clinics since the diagnosis of deafness may be suspected before the possibility of childhood autism is considered. Childhood autism is usually suspected when attention is paid to symptoms of the disorder such as the disturbed motility patterns and the tendency to over-react as well as to under-react to both auditory and other types of stimulation.

Complete or partial blindness can induce disturbed behavior often associated with mannerisms known as "blindisms." These blindisms involve manneristic gesturing with the hands in front of the face; they usually do not have the stereotyped quality of the hand flapping of autistic children. Furthermore, the blind children do show interest in their environment when their visual deficit is recognized by others and an attempt made to relate to them through non-visual means. The syndrome of childhood autism has been described in association with retrolental fibroplasia but not with other types of visual impairment.[86] Since retrolental fibroplasia is often associated with organic brain damage, there is reason to suspect that the autistic symptoms are associated with the latter condition rather than with the visual deficit *per se*.

Developmental aphasia (congenital auditory imperception)

When the autistic child first comes for diagnostic consideration, often the presenting problem is delay in the acquisition and deficiency in the use of speech. Therefore, a number of developmental disorders characterized by language disturbance must be considered. The effects of maternal deprivation or loss, emotional disorders and hearing deficit on the acquisition and use of speech have already been discussed. Language retardation as part of a general mental retardation will be considered below. A relatively rare but diagnostically troublesome developmental disorder which requires additional consideration is developmental receptive and expressive aphasia.[31] In both this disorder and in childhood autism there are abnormal responses to sounds, delay in the acquisition of speech, difficulty in its comprehension and use, and difficulties in articulation.[87,88] As speech is slowly acquired both aphasic and autistic children distort and invent words. Because of their difficulty in communicating and being understood,

aphasic children may develop secondary disturbances of relating and social responsiveness suggestive of the problems of autistic children. However, aphasic children do not develop the sensory hyper- and hypo-sensitivities characteristic of autistic children and they do show the capacity to relate by nonverbal gestures and expressions and they respond to the gestures and expressions of others.[89] Young asphasic children usually point toward a desired object whereas autistic children will not.[57,90,91] As speech is acquired, aphasic children rarely show the lack of "communicative intent" and emotion[92] and the *delayed* echolalia[90,93] characteristic of the speech of autistic children. When linguistic operations are translated into visual forms, aphasic children demonstrate comprehension whereas autistic children do not.[94] A curious and interesting finding is that there is a history of language delay in the parents or siblings in about one-third of the cases of both aphasic and autistic children.[90]

The differential diagnosis of childhood autism must include consideration of three additional conditions. While mental retardation, several organic brain syndromes, and certain types of seizure disorders may be distinguished from childhood autism, these three disease categories may also coexist with childhood autism.

Mental retardation

When childhood autism was first recognized as a disease entity, an attempt was made to differentiate it from mental retardation.[89] Terms such as pseudo-retardation were devised on the assumption that the retardation seen in autistic children was only apparent and due to the child's unwillingness rather than inability to perform on developmental or intellectual tests.[11,12] However, greater clinical experience with autistic children and recent follow-up studies have demonstrated that low scores on developmental tests or "untestability" in the early years of life may be predictive of retarded functioning later in life.[13,14] Autistic children not only will not, but actually cannot, perform many tasks.[95] The notion that autistic children have a primary affective deficiency[96] and good cognitive potential[45] has given way to the recognition that the cognitive deficiency in childhood autism is every bit as real as in mental retardation[90,97] and that approximately 75 percent of autistic children can be expected to perform throughout life at a retarded level.[98] Mental retardation and childhood autism can clearly coexist.[99]

Organic brain syndromes

The minority of autistic children who are not retarded usually do not reveal evidence from history or examination of definite central nervous system impairment. Of the majority of autistic children who are retarded, a number may show presumptive or definite evidence of organic brain damage or of one of the specific organic brain syndromes.[100,101] It should be emphasized that although attempts have been made to link autistic behavior with degenerative diseases such as Heller's syndrome,[102] childhood autism does not ordinarily follow the clinical course of a degenerative organic process.[89] Childhood autism does, however, occur *in association with* the sequelae of prenatal and perinatal complications,[103] neonatal conditions associated with brain damage such as retrolental fibroplasia,[86] infantile spasms,[16,18,101,104,105] cerebral lipidosis,[16] and metabolic conditions such as phenylketonuria,[31,63,96] Addison's disease,[106] and celiac disease[107,108] or infectious conditions such as congenital rubella.[87,109] Congenital rubella deserves special mention in that 8 to 10 percent of the children affected by it may show autistic symptoms[110] and in a number of classical cases of childhood autism the patients have been shown to have had congenital rubella.[109]

Seizure disorders

The alterations in consciousness associated with seizure disorders must be distinguished from the behavior of young autistic children. In some young children, momentary posturing and staring may simulate petit mal epilepsy, and electroencephalography is required to rule out a seizure disorder. In other young children, autism and a seizure disorder may coexist.[16,18] Seizure disorders are more likely to occur as autistic children become older. Twenty-five percent of a well-followed series began to have seizures between 11 and 19 years of age. Most of these children had normal electroencephalograms and neurologic assessment earlier in life.[13,90] Both grand mal[18,90] and psychomotor seizures have been described in autistic children.[104,111]

Prenatal and Perinatal Factors

The maternal age at the time of birth of autistic children does not differ from that of the general population.[104,112,113] While an excess of first-born autistic children in two-child families has been reported,[22,114] there is no relationship to birth order when families with three or more children are taken into account.[18,30,31,104,112,113] Early reports of

a highly significant excess of male over female autistic children (4:1)[114] have been confirmed in some studies[18,22,113,115,116] but not in other series, where male to female ratios of 2.8:1,[30,112] 2.6:1,[103] 1.7:1,[117] and 1.6:1[104] have been reported. It should be remembered that equivalent excesses of male over female will be found in general child psychiatric populations.[30]

Childhood autism does not seem to be associated with prematurity.[18,104,112,117,118] There have been a number of studies of the incidence of other prenatal and perinatal complications in childhood autism.[18,103,104,112,115,117,119,120] The findings from these several investigations are difficult to compare in that in some investigations siblings of the patients were used as controls,[103,112,119] while in other studies non-autistic "handicapped" children,[112] normal children[103,117] or so-called late onset psychosis patients[18] were used as controls. While several of these investigations have found a greater incidence of prenatal complications in the autistic than in the control group,[18,103,112,117] only one study reported a significant increase in prenatal complications in the autistic children.[117] The overall findings in respect to perinatal complications were similar. Again while several investigations found a higher incidence of perinatal complications in the autistic children,[18,103,112,119] in only one series was the increase in perinatal complications in the autistic children significantly greater than in the controls, and in this study unfortunately the diagnostic criteria for the patient group were vague and nonspecific.[119] When all prenatal and perinatal complications were lumped together there is a suggestion from four studies that there may be a significant association of such complications with childhood autism.[18,103,115,120] These findings must be viewed with caution because of the lack of uniformity of both diagnostic criteria for the children and assessment of importance of the prenatal and perinatal complications. Pollack and Woerner have discussed the methodologic problems in some of these studies.[121]

Family Background

Constitutional and genetic factors

With the exception of two studies,[113,122] neither an increased incidence of schizophrenia nor a history of childhood autism has been reported in the parents or non-twin siblings of autistic children.[18,20,22,89,114] Creak and Ini[113] found four probably psychotic siblings in 79 families and two schizophrenic parents out of 120 studied. Meyers and Goldfarb[122] found 8 percent of the siblings and 21 percent of the parents examined to be schizophrenic.

Studies of twins in whom one or both members of the pair are autistic are of interest for a genetic hypothesis for childhood autism. Vaillant reviewed the literature to 1963 adding two sets of twins,[123] and additional cases were considered by Rimland in 1964.[124] The most recent review of the literature on autistic twins included the cases considered by both Vaillant and Rimland and critically examined the evidence both for monozygosity and the diagnosis of childhood autism.[20] Satisfactory evidence for both the clinical diagnosis of childhood autism and the criteria for monozygosity was provided for only four out of 20 reported twin pairs. Of these four, one pair of monozygotic twins was concordant[125] and one was discordant for childhood autism.[126] One dizygotic pair was concordant[127] and one was discordant.[123] Allowing less stringent requirements for the clinical descriptions and the evidence for monozygosity, and excluding two twin pairs because of evidence of organic brain impairment and three other pairs where the literature reference was limited to a "personal communication to the author," the remaining 15 of the 20 twin pairs cited by Rutter[20] break down as follows: Out of ten presumably monozygotic pairs, eight were concordant[125,128-134] and two discordant[123,126] for childhood autism. Of five presumably dizygotic pairs, only one was concordant[127] and four were discordant for childhood autism.[113,123,135,136] It can be concluded that the available evidence from twin studies, though in a majority of cases technically imperfect, is suggestive of the possibility of a genetic determinant in at least some cases of childhood autism.

It is of interest to note that childhood autism has been described in diverse racial stocks including, for example, children in Finnish[137] and Japanese[138] populations.

Attempts to find chromosomal abnormalities in autistic children have been unsuccessful.[136,139] Studies reporting unusual dermatoglyphic patterns[140] and hand morphology[141] in some psychotic children with autistic features have yet to be replicated.

Family characteristics

Since the first description of autistic children in 1943,[3] the parents of the children have come under intense psychiatric scrutiny.[142] The original clinical description of the parents as being persons strongly

preoccupied with abstractions, limited in geniuine interest in people and emotionally cold so that the children experience a mechanization of human relationships,[89] has died hard.[50,143-145] Unconscious maternal hostility toward and rejection of the child who becomes autistic or schizophrenic has also been postulated.[146,147] More balanced appraisals have described the parents as being unusually "perplexed" and thus thwarted or ineffective in dealing with their psychotic child.[148] Such mothers have also been described as lacking in clarity of communication.[149] However, parental perplexity or unclarity may be secondary to the intense and often insoluble problems of raising a child with this kind of disturbance. A number of careful studies of parental emotional characteristics and child rearing attitudes have not confirmed assertions that the parents of autistic children are either unusually cold or aloof or have any other emotional or personality characteristics which would in any way predispose the autistic child to his disorder.[18,90,97,150,151] Other studies have also indicated that the extreme emotional stress of having an autistic child in the family may induce or precipitate emotional disorders in some susceptible parents[113] and that the professional assumption that there must be something wrong with the parents in order to have such a seriously disturbed child may also cause iatrogenic emotional disorder in the parents.[152]

Investigations which have utilized psychological test results to demonstrate psychopathogenic personality traits in the parents of autistic children[153] have frequently failed to consider the emotional context in which the tests are administered. For example, in a well-designed study Schopler and Loftin recently showed that out of anxiety parents of autistic chilren may appear to have a thought disorder on psychological testing if the testing is done in the context of their relationship with their psychotic child but not in the context of their relationship with the normal sibling of the psychotic child.[154] As accumulating clinical evidence has indicated that as a group the parents of autistic children are emotionally no different than the parents of normal or neurotic children, an attempt has been made to sustain the notion that nevertheless adverse environmental influences must have contributed to the development of the autistic symptoms. Thus, while the parents individually may be accepted as "normal," the possibility of family turmoil or some other disturbance in the family dynamics or parent-infant relationship at an early critical period of a child's development has been invoked.[7,8] However, no sufficient evidence has been presented and other studies have suggested a normal family structure.[30]

Since the first group of cases was described in 1943,[3] several references to the unusual intelligence of the parents of these children have appeared.[31,50,112,114] It should be noted, however, that intelligence may be tied to socio-economic status and that studies which have found increased intelligence in the parents of autistic children have also found the socio-economic status of the parents to be skewed toward higher levels.[20] Lotter[112] found, however, that the intellectual superiority of the mothers though not of the fathers was independent of social class and level of education. Two recent studies comparing the verbal intelligence of both the mothers and fathers of autistic children with that of parents of normal children where both groups were matched for socio-economic status found no difference in intelligence between the two groups.[155,156] Thus there is now some doubt about the earlier assertions that the parents of autistic children are unusually intelligent.

Considerable attention has been given to possible differences in the socio-economic status *per se* of the families of autistic children. Nine reports suggesting that autistic children are found in families whose socio-economic status is higher than that of the general population or of matched controls[3,18,22,30,112-114,151,157] were not confirmed by three studies, one of which studied the distribution of autistic and non-autistic psychotic children among five social classes,[158] one of which compared the families of autistic patients with matched non-autistic patients[159] and one of which compared the families of autistic patients with matched normal controls.[155] The finding that the socio-economic level of the fathers of autistic children is somewhat higher than that of fathers of brain-damaged children but not of the fathers of normal children[155] may very well be due to the fact that perinatal morbidity is likely to be greater in lower socio-economic levels.

In general it can be said that there is no compelling evidence suggesting that there are any significant or important differences in the parental characteristics or the family structure of the families of autistic children. The possibility that there is an overall increased incidence of autistic children in families of higher socio-economic status associated with higher parental intelligence is interesting though of no special clinical relevance

at present. Certainly this reviewer and others[159] have seen autistic children in families of all socioeconomic, ocupational, educational, intellectual, religious and racial backgrounds.

Epidemiologic Considerations

The comprehensive epidemiologic study of childhood autism by Lotter demonstrated a prevalence rate of 4.5 autistic children per 10,000 eight- to ten-year-old children resident in the County of Middlesex, England.[160] A smaller prevalence rate (0.7 per 10,000) was reported by Treffert (using different epidemiologic techniques and possibly different diagnostic criteria) in a population-based survey of three- to eleven-year-old children in Wisconsin.[157] Both figures can be considered minimal since autistic children younger than four years old and older than six years old are often misdiagnosed. At all events, childhood autism does not seem to be as rare a condition as is often popularly stated. Lotter pointed out that, based on his own survey of school-age children, there were as many educable autistic children as there were blind children in special schools in the surveyed population area.[160] Thus the autistic child represents a significant epidemiologic problem.

Prognosis

In approximately 7 percent[16] to 28 percent[98] of autistic children who had not been epileptic in early childhood a seizure disorder develops later. Approximately 75 percent of the autistic children are and remain mentally retarded.[17,98] Many of these may be "untestable" when seen in the preschool period[95] but repeated developmental testing with increasing age has demonstrated that "untestability" in early childhood is actually a prognostic sign of low intellectual functioning in the autistic child.[14] Those autistic children who have seizures or other indications of organic brain damage tend to be in the more retarded group of autistic children.[98,115] They also tend to be children whose language function remains severely undeveloped or impaired. It has long been recognized that failure to use language for communication by the age of five years implies a very poor prognosis for further intellectual and personality development.[13,17,27,50,161] Failure to use toys appropriately also signifies poor prognosis.[116] Thus, the autistic child who is close to his fifth birthday, is not using communicative speech (the speech may be limited to echolalia), does not play appropriately with toys, and who appears intellectually retarded or is untestable during the course of developmental evaluation has a poor prognosis indeed and is likely to require lifelong institutional care.[162]

For the minority of autistic children who are testable and show relatively normal intellectual function on developmental tests and who develop communicative speech before the age of five years the outlook is somewhat different. In the majority of these cases, a clearly defined schizophrenic psychosis with delusions and hallucinations does not develop.[98,163] Most of the children, however, do become extremely shy, introverted, passive, withdrawn, and schizoid.[33] Although not having delusions or hallucinations, some of these children do develop severe disturbances of reality testing such as is seen in the more covert forms of schizophrenia referred to as pseudo-neurotic or borderline states.[11,17,24] One series of cases[15,33] and several individual case reports documenting a transition from early infantile autism to a frank schizophrenia in late childhood,[2] adolescence[34] or adulthood[164] are of interest and suggest that further research on possible relationships between the two diagnostic conditions deserves consideration.[34] Although some of those autistic children who are not retarded and who do develop useful language before five years of age are able to live in society and to obtain employment,[165] it is to be emphasized that they represent a minority of the autistic population seen in early childhood and that even those children with a relatively good prognosis will usually have significant residual personality and cognitive impairments.[15]

Problems in Early Recognition

Several factors have complicated the recognition and diagnosis of childhood autism in the early years of life. First, pediatricians and practitioners of family medicine have not known what to look for since many descriptions of the illness have been couched in terms of psychoanalytic ego psychology[10] instead of providing clear-cut descriptions of behavior. While the former may be useful in the context of developmental ego psychology and even in the treatment of selected cases,[166] only an accurate description of the specific behaviors which constitute the syndrome of childhood autism permits accurate early diagnosis. The second problem confronting the physician is that many of the

symptoms of the autistic child are behaviors which are seen as part of normal development in normal infants and toddlers.[66] This "maturational lag"[1] has contributed to the serious difficulties in recognizing childhood autism during the first and second year of life.

In current practice many cases of suspected childhood autism are not referred for psychiatric evaluation until the fourth or fifth year because symptoms such as toe walking, hand flapping during states of excitation, hypersensitivity to sensory stimuli and idosyncratic play activities are either overlooked or passed off as immaturity. Until recently, psychiatric referral often has not been particularly helpful since many psychiatrists trained in adult psychiatry, and even many child psychiatrists trained in institutions where the emphasis has been upon the treatment of the older child, have not seen young autistic children.

A third problem in early recognition is that both psychiatrists and other physicians have focussed primarily on the disturbances of relating seen in autistic children. There has been a failure to appreciate the fact that the disturbances of relating represent only a part of the syndrome of childhood autism and that at least equal attention must be given to both the disturbances of motility and perception. Both the disturbances of relating and language may, in fact, not be seen during the first two years of life and failure to look for unusual motility patterns and sensory hyper- and hyposensitivities may result in missing the diagnosis.

A fourth problem is that childhood autism has frequently been viewed in an all or nothing context. Physicians have not been prepared for the fact that childhood autism may occur with degrees of severity which vary from case to case and that the autistic behavior may occur inconsistently in the individual patient. Thus as with most medical conditions childhood autism can be seen in very mild or in very severe forms. An autistic child may have adequate eye to eye contact and may desire to be held by his mother some of the time and yet show severe sensory hypersensitivities, hand flapping, whirling and echolalic speech. An autistic child may spend long hours in stereotyped perseverative play limited primarily to spinning objects and yet may come when called and be relatively responsive to the parent on occasion.

A fifth factor complicating early diagnosis is that the condition is often so bewildering to the parents that it is often impossible for the mother of a young child beginning to show autistic symptoms to articulate her concerns to her pediatrician or family doctor. She often feels guilty or ashamed of her child's behavior and it may be very difficult for the average mother to acknowledge the fact that her infant does not seem to be dependent upon her or that he has no desire to be with her. The autistic infant's preoccupation with sensory stimuli or his own body movements to the exclusion of his interest in his mother or his apparent aversion to being cuddled and loved frequently induces a profound loss of self-esteem in a young mother. She may then deny as long as possible her concerns about her infant's deviant development and when she does bring the infant to her physician's attention she may articulate these concerns in so guarded and confusing a way as to throw the physician off the track of accurate diagnosis. In other cases the mother's tendency to deny the more subtle aspects of deviant behavior in her infant may occur due to her lack of knowledge of normal child development.[167] Many young mothers are not aware at what age a baby should first indicate its desire to be picked up and held, when an infant should establish and maintain eye contact, and when an infant should begin to show a differential response to the mother or to a stranger.

With these considerations in mind, physicians responsible for the care of children during infancy may utilize the following approaches to the problem of deviant development. First, it is extremely important that the physician be thoroughly grounded in a knowledge of normal development in early childhood. The usual knowledge of the normal motor and language milestones must be supplemented by a thorough understanding of the normal sequence of development of the infant-mother relationship and social awareness. Second, as with any medical condition, there must be a high index of suspicion in the physician's mind. Many cases have been missed in the early years of life primarily because childhood autism has been considered a rare condition and has not been included in the differential diagnosis.

Once autism is suspected, it is necessary to bear in mind that the various symptoms of the disorder may only occur intermittently and, therefore, may not be present on any one examination. Hence it is necessary to spend considerable time with the young child showing deviant behavior and to

examine him under different conditions. The infant must be engaged in social play appropriate to his age in order to bring out the deviant ways of relating characteristic of the autistic child. However, if one sees the child only in circumstances of active involvement in social interaction with an adult, then the disturbances of motility and response to sensory stimuli may be missed. Frequently it is only when the autistic child is left alone that symptoms such as hand flapping, perseverative regarding of hand movements and bizarre tactile and visual exploration of the environment become apparent. Presentation of certain sensory stimuli can be helpful. A rapidly spinning child's top *may* induce hand flapping and bizarre states of excitation which would otherwise be missed on examination. The child should be tested with a loud sound capable of illiciting a vigorous startle response in a normal infant; the failure of the autistic child to respond to such a sound with more than an eyeblink is often impressive. Paradoxically, severe adversive reactions characterized by withdrawal, agitation or fear can often be elicited by vibration of a tuning fork (256 hz.).

It is not only necessary to examine the child on several occasions and under several different conditions, but it is also necessary that he be in a relaxed but alert state. If the child is sleepy and it is near nap-time, all symptoms of the disorder may be missed. As many young autistic children are extremely disturbed and frightened in new or strange settings, the physician may be confronted in his office with a screaming child whose great agitation precludes observation of any other behavior. It may be necessary to familiarize the child with the office over a period of time or to see the child at home.

Examination of the child is only part of the diagnostic process. A thorough history of the previous development must be obtained. It is most important that the mother be asked the proper questions and that she be asked them in the proper context. The physician must have a good relationship with the parent and must help her to feel that he is on her side in trying to understand what there is about her child's behavior that has troubled her and has created difficulties for her. It has been an unfortunate aspect of both psychiatric and pediatric practice to tacitly assume and to unwittingly convey to the parent that if a child has an emotional or behavioral disturbance, then it must somehow be the parent's fault. Such a communication to the parent, whether overt or covert, natuarally increases the parent's difficulty in articulating her concerns about the child and increases her tendency to deny significant behavior disorder in the child.

Once the proper relationship with the parent has been developed, the physician must then take the initiative in eliciting relevant information—for example, how the child responded to the introduction of solid foods, or when he began showing an anticipatory response to being picked up, or responded actively to pattycake or peek-a-boo. Many mothers will not spontaneously volunteer such information either because they do not realize that it would be of interest to the physician in his assessment or because they are not aware that the child has deviated from the norm.

Finally, the tendency of the physician to adopt a "wait and see" attitude when confronted with a problem of deviant behavior in early infancy deserves comment. Many mothers of autistic children have commented that they were preplexed, confused and disturbed by their infant's behavior as early as the neonatal period. Their attempts to draw the physician's attention to the child's deviant behavior in the early months of life were essentially rebuffed by the physician's reply that "it is to early to be concerned" or "he'll probably grow out of it" or "infants vary greatly in their behavior." The mothers continue to be worried while the "wait and see" period extends well into the third or fourth year of life. The physician's tendency to "wait and see" is frequently motivated by excellent intentions: much unusual behavior and temporary developmental lags in early infancy do indeed disappear with increasing age and the physician is reluctant to alarm the mother unduly by expressing his concern or by responding actively to hers when there is indeed a chance that the disturbing behavior may "go away." Unfortunately, the result of such practice is often to leave the mother with a sense of isolation and alienation. She finds herself alone with her concerns and she must come to conclusions of her own device about what is wrong with her child. These are often erroneous and lead her to deny a progressive developmental problem rather than return to her physician for adequate evaluation. In general, parents are relieved rather than disturbed by adequate consultation and diagnostic study of their child.

Neurologic and Electroencephalographic Examination

Neurologic examination of some autistic children is unremarkable[168] but "soft" neurologic signs such as poor muscle tone, poor coordination, clumsiness, hyperactive knee jerks, hypotonia, generalized hyper-reflexia, drooling, short attention span, hyperkinesis, hypokinesis, ankle clonus and strabismus have been reported in 40 to 75 percent of several series.[29,115,117,120]

Electroencephalographic findings are quite variable. Two reports of unusually low voltage EEG's suggestive of hyperarousal[18,64] were not confirmed in two other studies[169,170] when stimulus conditions were controlled. While some studies have reported 50 to 80 percent of the patients to have abnormal EEG's characterized by either focal or diffused spike, slow wave or paroxysmal spike and wave patterns,[117,169,171] other studies have reported less frequent EEG abnormalities.[18,45,120,168] In most of these investigations, the ages of the autistic children have varied widely at the time that the EEG's were recorded. In reports of the results, age was often not specified and it is quite possible that the higher percentages of abnormal EEG's are associated with older patients. This would be compatible with the increasing incidence of seizures with increasing age.[98] The clinical experience of this reviewer with autistic children under five years of age suggests that EEG abnormalities in young autistic children are very rare indeed unless there have been associated infantile spasms.

Neurophysiologic Studies

Because of the extreme lack of cooperation of autistic children, neurophysiologic studies have been quite limited in scope and number. Autistic children have a normal sleep cycle with normal amounts of rapid eye movement (REM) sleep.[134,172,173] However, the rapid eye movement activity of REM sleep is reduced in autistic children[174] and is similar to that found in normal infants,[175] suggesting a maturational defect.[176] While the transcephalic direct current potential is similar in autistic and normal children, an unusually high percentage of "DC bursts" are found in six- to thirteen-year-old autistic children and one- to five-year-old normal children.[108] Unfortunately, adequate controls for eye movement activity were not reported so that this apparently interesting maturational finding may only reflect the tendency of older autistic and younger normal children to have more vertical eye movements. The contingent negative variation (CNV) is intact in autistic children when two stimuli are paired together but the autistic children, unlike normal controls, do not show a differential response to slides of familiar and strange faces.[177] This does not seem to represent a neurophysiologic abnormality, since the basic ability to establish a CNV is intact, but rather reflects the ordinary clinical experience that autistic children do not show adequate differential responses to strangers and do not participate in social interaction.[178]

Studies of auditorily evoked responses during sleep have revealed only marginal differences between autistic children and controls and have been characterized by great variability from subject to subject.[179-181] One study of evoked responses to flashes and clicks in waking autistic children is inconclusive since no statistical analysis of the data was presented.[182] An inadequate galvanic skin response to both auditory and visual stimuli has been demonstrated in autistic children.[183] This finding is consistent with the clinical observation that autistic children do not show an adequate startle response. It was not possible, however, to replicate the finding by using change in heart rate as the experimental measure.[184] Increased variability in the heart rate has been reported but adequate control of activity level and stimulus conditions under which autistic and normal children were observed was not documented.[185] Thus the assertion that evidence was found for brain stem dysfunction is somewhat tenuous. However, other evidence implicating a brain stem disturbance has been found. Three separate investigations have demonstrated a consistent suppression of vestibular nystagmus in autistic children.[186-188] It should be emphasized that the suppression of vestibularly induced nystagmus has only been demonstrated under conditions where visual fixation is possible.[188] Thus a theory of vestibular dysfunction in childhood autism[35] may require modification to take into account a neurophysiologic defect involving the vestibulocerebellar axis since the strong proclivity of autistic children to suppress vestibular nystagmus through ocular fixation might be explained by the role of the cerebellar roof nuclei in the suppression of nystagmus through fixation.[189] The finding of primitive neck and labyrinthine righting responses in eight- to twelve-year-old schizophrenic children is also suggestive of vestibulocerebellar dysfunction.[190] However, a history of early autistic development was not documented for the children in the latter study.

Metabolic, Biochemical and Hematologic Studies

Indoleamine metabolism has received considerable attention in studies of autistic children. The results, while of a preliminary and often inconsistent nature, suggest that this field of investigation requires further serious study. One report of decreased urinary excretion of 5-hydroxyindoleacetic acid in response to a tryptophan load[191] was not replicated in a later study.[192] Heeley and Roberts studied the ratio of urinary 3-hydroxy-kynurenine to 3-hydroxyanthranilic acid in response to tryptophan load and reported results suggesting decreased availability of pyridoxine.[193] Sankar et al[194] reported an excessive amount of indolic substances in the urine of five- to sixteen-year-old hospitalized schizophrenic children. However, not enough clinical information is provided to determine whether these children would be considered autistic as described in this review. In contrast to Sankar's findings, Jorgensen et al found a significant reduction in urinary excretion of tryptophan in three- to six-year-old psychotic children.[195] Bufotenin (N,N-dimethylserotonin) has been found in the urine of some but not all autistic children.[196]

Another group of studies has focused on the amount of serotonin in the peripheral blood and its relation to blood platelets. Schain and Freedman found that 25 percent of a group of 23 children diagnosed as autistic had elevated blood serotonin levels.[197] Ritvo et al[198] found a significantly greater amount of whole blood serotonin in five autistic children 36 to 47 months of age than in seven age-matched normals; there were no significant differences between older autistic children and age-matched controls. The platelet count showed a slight decrease in normal children between two and eight years of age while it increased in autistic children through that age range, but the differences did not reach significance.[198] There were no differences in circadian rhythmicity for either blood serotonin or platelets which might influence these results.[199] Prolonged administration of L-dopa decreased the blood serotonin concentration in three out of four autistic children and there was a tendency toward an associated increase in platelet counts. However, there was no corresponding change in the clinical course of the disorder[200] or in the sleep patterns of the children.[201] Chronic oral ingestion of the serotonin precursor 5-hydroxytryptophan had no effect on behavior in two autistic children and caused some increase in REM sleep time and also in the rapid eye movements in REM sleep,[202] an effect that also occurs in normal persons.[203]

A related group of investigations has been concerned with the concentration of serotonin within blood platelets. Sankar et al found that the uptake of serotonin by platelets was less in schizophrenic children than in control hospitalized children.[194] Boullin et al[204,205] reported an increased efflux of serotonin from the platelets of autistic children. The same group did not find any unusual differences in uptake or loss of dopamine from platelets of autistic children.[206]

A number of other miscellaneous studies have been made. The plasma cortisol level, eosinophile count, and histamine wheal test are not remarkable in autistic children.[108] Plasma and erythrocyte cholinesterase activity,[207] and serum magnesium,[208] copper ceruloplasmin and ascorbic acid levels[209] are within normal limits. Baseline free fatty acid levels and the plasma free fatty acid response to glucose ingestion are within normal limits except for increased variability in the baseline plasma free fatty acid level[210] which may be associated with greater variability of daily caloric intake.[211] In one study, both plasma and red blood cell inorganic phosphate were reported to be elevated.[212] One report of pituitary hypofunction (reduced secretion of gonadotropins, ACTH and TSH) in children with the onset of illness in the first three years and behavior suggesting autistic development deserves an attempt at replication.[213] In one study of peripheral blood smears in schizophrenic children, an atypical leukocyte pattern was described.[214] The types of abnormalities reported were similar to those associated with antibody production or with response to viral infections and allergic sensitivity and could not be distinguished from those found in blood smears of children with colds or asthma. The results may therefore merely reflect an increased susceptibility of schizophrenic children to infectious disorders. Studies from one laboratory reporting a serum factor which increases the susceptibility of mice to seizures[215,216] deserve further investigation in view of the increased incidence of seizures in autistic children.[13,111]

Treatment

At the beginning of any discussion of the treatment of autistic children it should be emphasized that there is no specific treatment for this disorder

and that in spite of strong claims by partisans of particular treatment approaches and a tremendous amount of dedicated effort which has gone into these approaches, no single treatment has stood the test of time.[217] The many different approaches which have been attempted have included family therapy, psychotherapy and counseling for the parents of the autistic child, psychotherapy for the autistic child himself, behavior modification, speech therapy, various forms of special education, the day treatment center approach, residential treatment, medication with a number of different psychotropic drugs, vitamins, electroconvulsive therapy, sensory stimulation, and sensory isolation.

Since autistic children vary greatly in their intellectual capacity, use and understanding of speech, general developmental level, age at time of treatment, level of personality development, general severity of the illness, and family circumstances, it is not surprising that some of the above treatment approaches have been helpful in certain cases of childhood autism but not in others.[27,218] The response to treatment is determined primarily by the degree of impairment and only secondarily by the type of treatment in the individual case.[116] At best, any one of the various types of treatment has been able to ameliorate but usually not eliminate certain specific symptoms or deficits in some autistic children; the children, though improved in a specific respect remain definitely autistic.[162]

The best approach to treatment is a flexible one that can be constantly adapted to the changes in developmental level, symptoms and capacity to communicate and learn which take place over a period of years.[219] The parents and the patients both benefit most from an approach that provides long-term management and guidance[220] and recognizes that spontaneous improvements and regressions are likely to outweigh the influence of the most optimistically presented treatment plan.[17]

With these reservations, some of the approaches to treatment will be discussed.

Therapeutic work with the parents

Attempts to treat the autistic child through either treatment of his parents[145] or isolation from his parents[146] were based on hypotheses that childhood autism was entirely of psychogenic causation, the ultimate cause being the psychopathology of the parents. Such notions are no longer accepted by the majority of serious investigators of this illness and are now only of historical interest. However, they should serve as a warning of the ease with which the parents of ill children can be scapegoated by well-meaning professionals.[152] As the psychogenic hypothesis of causation has given way to mounting evidence that childhood autism is an innate condition with which the child is born and involves some yet poorly understood central nervous system dysfunction which interferes with the child's capacity to correctly perceive his environment, attempts to engage the parents in psychotherapeutic work have given way to more helpful parental counseling.[220] Such counseling is useful when directed both at the very difficult management problems presented by the autistic child and at helping the parents with the guilt and loss of self-esteem engendered by having a child who does not participate in ordinary parent-child relationships.[221,222] Earlier attempts to view and treat the parent as the cause of the child's illness[7,145,223,224] have given way to modern treatment approaches which have actually found the parent, when given proper counseling and support, to be a major asset in the treatment and management of the autistic child.[221,225,226]

Psychotherapy

Considerable attention has been given to individual psychotherapy with the autistic child.[6,7,138,218,224,227-230] With the passage of time such efforts have become confined to isolated treatment centers[166] due to the fact that either extravagant claims that psychotherapy is the treatment of choice for all such children or that it is completely useless have been made. The common error made by both those who have advocated and those who have disparaged the effectiveness of psychotherapy for these children is that they have failed to emphasize the important and striking clinical differences between one autistic child and another and the effect that these differences have upon the outcome of psychotherapy. For example, a study purporting to demonstrate that operant conditioning is more effective than play therapy was carried out on a group of autistic children suffering from profound developmental retardation.[231] Naturally, expressive play therapy would be doomed to failure in such a group. Likewise, extravagant claims that psychoanalytically based psychotherapy could be effective with the profoundly retarded type of autistic child have been universally disappointing.

There is, however, a minority of autistic children who develop communicative speech relatively early in life and who do not suffer from a profound

developmental arrest. These children do develop an organized and complex personality structure and have an active fantasy life; they have a psychic structure which can be treated effectively by psychonalytically or dynamically oriented psychotherapy.[232] Even with this particular type of autistic child there must be modifications of classical dynamic expressive psychotherapy.[228] For example, it has been shown that these children require a great amount of structure, predictability and limits in the treatment situation as they do in their life in general and that the effectiveness of treatment depends in part upon the clarity of the structure provided.[233]

In general, it is important to evaluate the degree of retardation, current developmental level, and availability or unavailability of speech for communication before recommending the treatment of choice for any particular autistic child. In some cases the treatment of choice is clearly psychotherapy. It should be emphasized, however, that this form of treatment is useful in only a minority of cases and may improve the child's ability to relate while laying bare his basic cognitive and language deficits.[234]

Behavior modification

Partly because psychotherapy can be applied to only a small minority of autistic children, there have been numerous attempts at using behavior modification as a treatment. Behavior modification utilizes operant conditioning techniques with either positive (food, praise) or negative (pain, punishment)[235,236] reinforcement. While both greater[231, 237-242] and lesser degrees[243,244] of success in carrying out this type of treatment have been claimed, the data from most of the studies indicate that any positive response to treatment is limited to the period of time during which the treatment is maintained and does not generalize readily beyond the specific experimental conditions[44,218,245-247] unless the treated child has already shown greater promise before the beginning of the treatment.

A recent follow-up study by the group most highly identified with behavior modification of autistic children[248] actually shows that relatively minor changes in autistic self-stimulatory behaviors and echolalic speech occurred during the course of therapy and that while there were increases in appropriate verbal behavior, social behavior and play, the best performance in these areas was at such a low level that the children would still be considered severely autistic by any clinical standards. Furthermore, on long term follow-up examination it was found that those gains made during the treatment were not well sustained. It has also been demonstrated that behavior modification can reveal the very limited capacity to respond in an adaptive and appropriate way even when the conditioning induces a high degree of motivation in autistic children.[243,249]

As with psychotherapy, behavior modification is appropriate for those autistic children with specific symptoms at a specific developmental level. In certain cases it can make an unmanageable autistic child more manageable[250-253] and has been used to reduce the amount of self-destructive behavior in certain individual autistic children.[133,235,236,254] It must be emphasized, however, that behavior modification is in no sense a treatment of the child's autism but is merely a way of reducing temporarily the amount of certain undesirable behaviors. The conditioning procedures involved in behavior modification can make an autistic child more manageable, and at times this is a worthwhile goal. However, it must be emphasized that the more manageable child is no less autistic.

Speech therapy

Considering the severe deficit in the acquisition of useful speech in most autistic children, the possibilities of speech therapy have received scant attention.[20] Most clinicians working with autistic children agree, however, that while some autistic children may have a primary language problem,[90,255] the failure or delay in speech acquisition cannot be treated as an isolated deficit.[222] Attempts to develop useful speech through techniques of operant conditioning have often been unrewarding. Even though the child may be conditioned to emit words in response to reward, this procedure only occasionally facilitates the use of speech for communication in these children.[222] Other workers are attempting to develop treatment plans which do emphasize meaningful communicative speech; "speech therapy," therefore, is practiced in the context of a total assessment of the child's perceptual,[256] communicative and cognitive,[52,257] and developmental handicaps.[258,259]

The therapeutic milieu and special education

Special education, often referred to as milieu therapy, is perhaps the most widely practiced approach to the treatment of autistic children. The particular procedures and treatment philosophies

vary from center to center[260] and generally tend to draw upon techniques used in psychotherapy, behavior modification[244,246,252,261] and speech therapy[262] with autistic children. Many centers for the special education of autistic children add parent counseling to comprehensive treatment programs and may involve the parents directly in the treatment of their children. Thus the milieu therapy or special education approach tends to be eclectic and pragmatic.

The advantages of this approach are that it does not attempt to fit all autistic children into the Procrustean bed of one or another particular treatment approach. Rather the emphasis in special education has been to recognize the pronounced inter-individual variability of autistic children and to adapt a particular educational and therapeutic program to the needs of the individual autistic child.[263] One important aspect of variability within groups of autistic children is intellectual potential.[264] Even in those settings with the most intensive treatment programs, autistic children with very low intelligence quotient do not do well.[244,264] However, special education does improve those autistic children with higher IQ's.[98,264] Hence a most important aspect of the initial assessment of an autistic child is that of his developmental level at the time of assessment.

Special education programs for autistic children may be carried out in schools,[252] in day treatment centers[265,266] or in residential treatment settings.[267] There is no evidence that residential treatment which involves separation of the child from his parents and family is any more effective than day treatment approaches which are less expensive and may produce better results.[234] However, there is a need for both types of programs; the decision to place the child in residential treatment as opposed to day treatment requires detailed consideration of the needs of the individual autistic child and his family. For example, if the child's difficult behavior is causing a depression in the mother so severe that she is unable to function well with the child or with his normal siblings, then it might be well that he be treated out of the home situation. If the child's self-destructive behavior is taxing the family's endurance then he might better be treated in a residential setting. On the other hand, if the parents are coping well with their autistic child's deviant behavior or if during the course of the diagnostic evaluation they show the capacity to respond effectively to counseling directed at better management of the child, then there is no reason to remove him from the home.[268,269] Adequate and complete assessment of the results of the special education approach to the treatment of autistic children is yet to be completed but several studies are in progress and some of the preliminary findings suggest that, while far from being a treatment of choice, special education is worthy of trial.[260]

The special education of the autistic child cannot be separated from the severe problems these children have in relating both to their peers in whose company they must learn and to their teachers who would educate them. Thus effective special education depends upon corrective socialization, a process which is carried out both in day treatment centers and in residential treatment. A sensitive and understandable account of corrective socialization in a residential setting can be found in the work of Goldfarb and his colleagues.[267]

Medication

Almost every conceivable psychotropic medication has been used with autistic children. The classes of medication have included sedatives, antihistamines, stimulants, major and minor tranquilizers, anti-depressants, psychomimetics and anti-Parkinsonism drugs.

As with psychotherapy, behavior modification, special education and speech therapy, no single medication or class of medication has made autistic children any less autistic. Nor has any medication or class of medication proven successful in removing any particular symptom of the autistic syndrome. Some drugs, however, have shown promise in ameliorating or partially controlling nonspecific behavior complicating the autistic developmental process. In particular some autistic children tend to be hyperactive, intractably restless, irritable, and over-responsive to all forms of environmental stimuli. In these cases and also with the sleep disturbances that sometimes complicate the management of these children, some of the major tranquilizers can be of help.[270] Other autistic children are characterized by a torporous lethargy and underactivity, and a few attempts at treatment with psychoactivating drugs have been reported. Before considering individual drugs, it should be noted that, just as with psychotherapy or behavior modification, the less impaired children respond best to drug therapy.[271]

The use of barbiturates for sedation in autistic children is generally not advisable. As is often true in young children in general, the barbiturates tend

to have a paradoxical stimulating effect. The antihistamine diphenhydramine often provides a more effective sedation. The minor tranquilizers deanol, hydroxyzine and meprobamate have been tried extensively with autistic children and generally are of little value. The phenothiazines prochlorperazine,[272] chlorpromazine,[270] and (in my personal experience) thioridazine can be useful in controlling excessive degrees of agitation and irritability. Reserpine has also been used for tranquilization[132] but offers no advantage over the phenothiazines.

For the withdrawn anergic type of autistic child, neither methylphenidate nor amphetamine derivatives have proved useful (personal experience). The piperazine phenothiazine, trifluoperazine, has been reported to reduce withdrawal and affective blunting and to increase motor initiative in some very young mute, retarded and anergic autistic children.[271] The butyrophenone derivative trifluperidol,[273] the thioxanthene derivative thiothixene,[274] a member of a class of drugs with actions similar to the piperazine type of phenothiazines, and the indol derivative molindone[275] have all been reported to have a similar combination of antipsychotic and "stimulant" effects. It should be emphasized that none of these medications has been shown to have any lasting effect and that at best they take the edge off difficult behavior when used as an adjunct to attempts at corrective socialization and special education.

A number of other drugs have been tried. The tricyclic anti-depressants imipramine[276] and nortriptyline[277] do not appear to be useful. L-dopa, which reduces the tremor in Parkinson's disease, has no effect on the motility disturbances nor on the general clinical course of childhood autism.[200] The behavior of autistic children is not affected by 5-hydroxytryptophan, a serotonin precursor.[202] Methysergide is a methylated derivative of LSD, which is used in the prophylactic treatment of migraine headaches. Its effect on 11 very young retarded schizophrenic children was a complex mixture of stimulation, disorganization and sedation; the sum total of drug effect could be considered therapeutic in only two cases.[278] Curiously, the psychotomimetic drug LSD-25 has also been used to treat autistic children.[279] Two reports suggesting that the drug increased social responsiveness[280,281] contrast with one study which emphasized the rapid mood swings from elation to depression, the anxiety, the flattening of affect and the auditory and visual hallucinations and decreased alertness which were induced in most of the children.[282] A recently completed study indicates that while positive changes in affect occur, they are of a highly variable and transient nature and are accompanied by diminished responsiveness.[283] The evidence to date throws doubt on the usefulness of this psychotomimetic agent as a therapeutic adjunct in the treatment of childhood autism.

Recent claims that high dosages of single or multiple vitamins—so-called megavitamin therapy—have a therapeutic effect on autistic children deserve special mention. As of the time of this writing it must be emphatically stated that no scientifically conducted, adequately controlled studies of the effect of multiple vitamins or any single vitamin have appeared which have in any way supported the claims of therapeutic effectiveness of medication of this type. The only well controlled scientific study yet published in this general area demonstrated that niacinamide had no therapuetic effect in a group of children four to twelve years old with the symptoms of childhood autism.[284]

Other treatment attempts

Finally, several miscellaneous treatment attempts deserve mention if only to point out how the intractability of this illness has driven clinicians to extremes of therapeutic ingenuity and tenacity. Perhaps influenced by the severe sensory hypersensitivities and hyposensitivities of the autistic child, experimental approaches to treatment have been based on both sensory stimulation in the form of intense human contact,[79] vestibular and proprioceptive play[285] or bodily contact and massage,[286,287] and sensory isolation.[288] The therapeutic effect of these divergent treatment attempts has been minimal considering the great investment of treatment time and effort involved, and sufficient replication has not yet been done. Finally, it should be mentioned that electroconvulsive therapy has been attempted[289] without significant or lasting benefit.[20]

Theoretical Considerations

Childhood autism is characterized by a profound failure of sensorimotor integration[66] complicated by serious disturbances of language and cognition[90] and human relationships. This disorder has its onset early in the first three years of life[1] and usually results in lifelong crippling distortions of the personality and intellectual development.[15,98,163] Earlier descriptions of this childhood illness stressed the disturbances of relating,[3]

whereas accumulating clinical evidence has emphasized the importance of the motor,[11,12] perceptual,[34,47,49,290] and cognitive and language impairments.[90,291] The unique defect of sensorimotor integration found in this behavioral syndrome is characterized by a faulty modulation of sensory input and motor output.[35] The former is manifest in both hypo- and hypersensitivity to sensory stimuli and the latter in a number of bizarre motility patterns. These patterns are characterized by both brief states of catatonic inhibition and by repetitive stereotyped motor patterns that often occur as part of general states of excitation induced by internal and external sensory stimuli. While many of these strange motor acts appear to provide the child with a considerable measure of self-stimulation,[68,292] the impaired ability of autistic children to use sensory input to make perceptual discriminations in the absence of feedback from their own motor responses[47] suggests that the bizarre and repetitive motor output may actually be a compensatory activity which helps the autistic child to make *sense* out of *sensation*. Some clinical studies have stressed the primacy of the sensorimotor dysfunction[66] while others have focused on the language impairment and cognitive aspects of the disorder.[90,97] It should be noted, however, that the onset of the disorder may occur at birth and that the earliest symptoms necessarily reflect deviant responses to sensory stimuli and deviant motility at a time when the cognitive and language impairments have not yet become manifest.[1]

The cause of this illness is unknown.[97] However, since so many of the symptoms represent distortions or lags in the normal maturational sequence,[1] an impairment in the basic mechanisms controlling the timing and sequencing of the developing control of motor output in relation to sensory input is implied.[66,293] There is meager evidence (from twin studies) that in some cases this disturbed maturational mechanism may be on an hereditary or an early congenital basis but many cases are associated with other conditions representing a variety of insults to central nervous system function. In all events, childhood autism is clearly a behavioral and emotional disorder based on some type of organic brain impairment and is not of psychogenic origin.[21]

This is not to say, however, that treatment directed at improving the capacity of the child to function emotionally in a human environment cannot be helpful both to the child and his family. Such an approach is not specific and should be considered only as one of several possible modes of treatment. There is in fact no specific treatment and it is of the greatest importance that treatment planning be directed at the specific deficits and the developmental limitations of the individual case. Particular attention should be given to the child's capacity to use language and to the child's actual intellectual potential. Repeated developmental examinations over a period of time are often helpful in establishing the child's true basal intelligence.

Finally, the relationship of childhood autism to adult psychiatric disorders deserves consideration.[294] Childhood autism is the earliest developmental manifestation of psychosis, and a number of students of this disorder have used the term *infantile or childhood psychosis* as an appropriate epithet for this condition.[15,16,18,22] Assertions that childhood autism may also be the earliest manifestation of schizophrenia[32,45,89] are not incompatible with the recognition that childhood autism is *phenomenologically* distinct from schizophrenia of later childhood and adult life.[18,163,294] Although the phenomenologic features of infantile autism and of schizophrenia are distinct, symptoms suggesting underlying perceptual disturbances in relation to motility in both conditions[34,35,66] and reports indicating the possibility of progression from an early infantile autism to a later schizophrenia[32,33,164] suggest the importance of further research on this aspect.

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This review of childhood autism is neither exhaustive nor complete. An annotated bibliography covering the literature on early childhood psychosis between 1964 and 1969 contains over 400 references.[295] The comprehensive review of childhood schizophrenia and allied conditions by Ekstein and his colleagues[296] covers the literature from 1946 through 1956 and contains over 500 bibliographic citations. In addition to the constraint imposed by the sheer magnitude of the literature, the following limitations have been placed on this review. An attempt has been made to reduce the redundancy that necessarily accrues from multiple and repeated presentation of the same work of a given author, research laboratory or treatment center by limiting citations to those which either represent unique findings or hypotheses or else comprehensive reviews of a particular investigator's

earlier work. An attempt has also been made to limit the citations to those in which the authors are dealing with childhood autism in the sense that this behavioral syndrome has been defined and described in this review. A brief perusal of the bibliography will quickly demonstrate that perhaps more of the titles refer to "childhood schizophrenia," "childhood psychosis" or "infantile psychosis" than to childhood or infantile autism. The problems of terminology have been considered in the body of this review. Articles could not simply be omitted on the basis of the terminology employed without omitting valuable material that is actually pertinent to the subject of childhood autism. Unfortunately many authors have failed to give a complete description of their patients. Therefore an attempt was made to include those articles in which those who wrote them indicated in one of the following ways that the subject matter related to autistic children: (1) a sufficient description of the patients was given to indicate that a reasonable amount of autistic symptoms was present; (2) the onset of the psychotic illness occurred before the child was five years of age and there was some indication that autistic symptoms or deviant development were present before three years of age; or (3) the literature references cited indicated that the authors were cognizant of the clinical syndrome of childhood autism. In a few instances where these criteria were not met but the article nevertheless merited inclusion, a relevant qualification was made in the text.

The reader's attention is called to several earlier reviews. An older, very comprehensive review written from a psychoanalytic and psychodynamic point of view by Ekstein and his colleagues[296] is very useful. A more recent and shorter review by Reiser[8] also emphasizes the psychoanalytic and psychodynamic point of view. An excellent review by Rutter[20] and a recent review by Hingtgen and Bryson[297] deal with all aspects of childhood autism from a more descriptive phenomenologic and pragmatic point of view. Rutter has provided shorter reviews of research[291] and follow-up studies.[98] Two reviews limited to therapeutic considerations are also helpful.[218,247]

Two symposia on childhood autism, one held in Indiana in 1968[298] and the other in London in 1970[299] deal with diagnostic, etiologic, phenomenologic and treatment aspects of childhood autism. Several books on childhood autism also merit the reader's attention. The book edited by Wing[300] provides useful information on the clinical, educational and social aspects of childhood autism. The monograph by O'Gorman[301] provides helpful clinical material. Hermelin and O'Connor[47] have written an excellent book summarizing their own psychologic research as well as the general field of psychological experimentation with autistic children. Goldfarb's monograph on childhood schizophrenia[29] is a sensitive clinical study of children who are essentially autistic and is also a good introduction to the earlier literature concerning the relative importance of organic and psychogenic factors.

A recent thoughtful and sensitive book by Dr. Lorna Wing[302] has been written specifically as a guide to parents of autistic children; it will also be of considerable use to physicians and other professionals concerned with the management of autistic children.

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Refer to: Sickle cell disease—Medical Staff Conference, University of California, San Francisco. Calif Med 118:48-55, Apr 1973

Medical Staff Conference

Sickle Cell Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* *The main purpose of these weekly Medical Grand Rounds, as all of you know, is that of continuing education for the members of this campus community, including students, house staff, faculty, and members of the medical profession and other health science professionals in the Greater Bay Area, and through the intermediary of television and videotapes, for an audience throughout Northern California. The topic to be discussed today is that of sickle cell disease. The case summary of the patient will be presented by Dr. Alan Engelberg.*

DR. ENGELBERG:† The patient is a 27-year-old black man, a musician, who was admitted 9 October 1972 for the second time with a two-day history of severe neck, knee, chest and back pain. At age two, the patient was thought to have rheumatism and growing pains. However, at age four, hemoglobin electrophoresis revealed the presence of hemoglobin ss. He has had chronic anemia with a hemoglobin of approximately 11 grams per 100 ml throughout his life and has required transfusions in the past for acute hemolytic episodes. His crises now occur approximately every two months, are manifested by severe knee, back, chest, bone or abdominal pains, and seem to be triggered by respiratory tract infections, exercise or stress. The patient had increasing pain that he said was typical of his sickle crisis pain for two days before admission, and fever up to 38.5°C (101.3°F). His past medical history includes numerous admissions to hospital for sickle cell crises. He was seen here for the first time in September of this year. He has had pneumonia three times. He had appendectomy and cholecystectomy at age 17.

His mother was tested and found to have sickle trait; his father was never tested and his sister is negative for hemoglobin s. His medications include empirin with codeine and folic acid. Review of systems revealed that he has had frequent respiratory infections and one to two block dyspnea and claudication on exertion. He recently had trouble with a left eye stoma.

On admission physical examination revealed he was in severe pain. Blood pressure was 126/72 mm of mercury, pulse 92 per minute and regular, temperature 38.7°C (101.4°F) and respirations 14. The sclerae were slightly icteric. The fundi could not be visualized because of pupillary con-

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striction. Small lymph nodes were palpable in the posterior triangle of the neck. The chest was clear. Cardiac examination revealed a regular rhythm and a soft systolic ejection murmur along the left sternal border. The abdomen was flat and nontender; no masses were palpable; bowel sounds were present but decidely diminished. Multiple scars were evident over the pretibial areas. The joints had a full range of motion but severe pain was elicited when the knees were flexed. Results of neurological examination were within normal limits.

Hemoglobin, which was 11.4 grams per 100 ml on admission, was 8.7 grams October 23. On admission, the hematocrit was 34.7 percent, mean cell volume 84, mean cell hemoglobin 31 and mean cell hemoglobin concentration 32.8; 7 percent reticulocytes were noted. The platelet count was 267,000 per cu mm. Leukocytes numbered 10,800 per cu mm, with 71 percent neutrophils, 22 percent lymphocytes and 7 percent monocytes. Examination of the smear revealed 16 nucleated red blood cells per 100 white cells and pronounced anisopoikilocytosis with a moderate number of sickle cells. Serum iron was 66 micrograms per 100 ml and iron-binding capacity 230 micrograms per 100 ml. Serum vitamin B-12 was 570 picograms per ml and serum folate was 10 nanograms per ml. The bilirubin was 2.4 mg per 100 ml, of which 0.8 mg was direct reacting. Serum glutamic oxaloacetic transaminase (SGOT) was 45 units and lactic acid dehydrogenase (LDH) 540 units. Urinalysis revealed 3 plus proteinuria and a specific gravity of 1.004. Cultures of blood, sputum and urine were all negative.

The electrocardiogram was normal. An x-ray film of the chest on admission showed a questionable area of atelectasis in the right lung field which was noted to have resolved by October 23. Films of the spine revealed increased trabecular markings consistent with the changes of sickle cell disease.

The patient was treated with intravenous fluids, nasal oxygen and large doses of morphine. He left the hospital October 23 against medical advice, when his pain had resolved.

DR. SMITH: *Thank you, Dr. Engelberg. The patient is unable to be here for presentation this morning. I would like to call on Dr. Michael Messer to open the discussion concerning this patient and his specific problem. Dr. Messer joined our faculty here a few months ago as an Instructor in Medicine and as a member of the Division of Hematology at Fort Miley Veterans Administration Hospital.*

DR. MESSER:* Thank you, Dr. Smith. This case is typical of sickle cell disease except for one point, and that is that the initial hemoglobin concentration is rather high. Most of our patients with sickle cell disease usually have a hemoglobin of about 8 grams per 100 ml. I would have been interested to see what a more recent electrophoresis would show. It is possible that this patient does not have homozygous sickle cell disease.

Few diseases have made so auspicious an entrance into the medical and scientific world as has sickle cell disease. From 1949 to 1956, a whirlwind of scientific activity yielded Pauling's[1] discovery of the abnormal electrophoretic mobility of hemolysates of sickle hemoglobin, Harris'[2] description of tactoids in the deoxygenated suspension of this abnormal hemoglobin, and finally the work of Ingram[3] demonstrating that one amino acid substitution in the beta chain of sickle hemoglobin distinguished it from normal hemoglobin. In this way hemoglobin s has become the prototype of a molecular disorder and the scientific excitement has never waned. In fact, today there are over a hundred known abnormal hemoglobins. However, despite its elegant beginnings and our sophisicated state of molecular biology, the mortality and morbidity of sickle cell disease and its variants have changed very little. In some ways our knowledge of the pathophysiology of this disease has been at a standstill. Today we are not certain what sequence of events in the microcirculation ultimately leads to tissue infarction, the hallmark of this disease. This lack of knowledge has manifested itself in a continuing record of inadequate treatment, where the best the physician has come to expect is palliation. Some very recent approaches to therapy will be touched upon later.

In discussing sickle cell disease, I am proceeding upon the assumption that the fundamental abnormality is the sickle hemoglobin and that, with certain exceptions, the more hemoglobin s a pation has per red cell the more apt the patient is to have severe disease. At first glance, this would appear to be *a priori,* but it is possible that other mechanisms aside from the red cell—such as

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inadequate humoral and cellular immunity against infection, increased thromboplastic activity, and even abnormal vessel endothelial swelling and proliferation—may play a role in the diffuse pathophysiology of the disease.

It is becoming increasingly clear that in any given patient with sickle cell disease there are two red cell populations. The major population are those cells that assume a sickle shape when deoxygenated, but which are capable of resuming a normal discoid shape upon reoxygenation. The minority are those cells which retain their sickle shape even in the well oxygenated environment. The latter cells have been aptly called the irreversibly sickled cells and constitute from 5 to 25 percent of the circulating red cell population. These two red cell populations reflect a continuum of the same molecular disorder, the irreversibly sickled cell being the end result of either an infinite number of sickling-unsickling cycles or prolonged sequestration in a noxious environment. I will elaborate in more detail about the irreversibly sickled cell later.

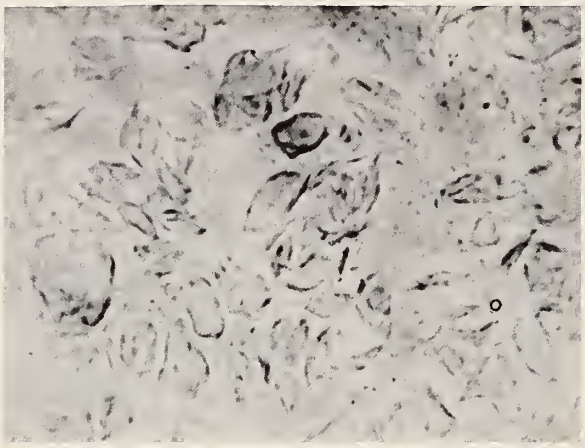


Figure 1.—Hemoglobin tactoids formed in stroma-free solutions of deoxygenated hemoglobin S. Phase microscopy × 775. (From Harris JW.[2] Reprinted with permission of the publisher.)

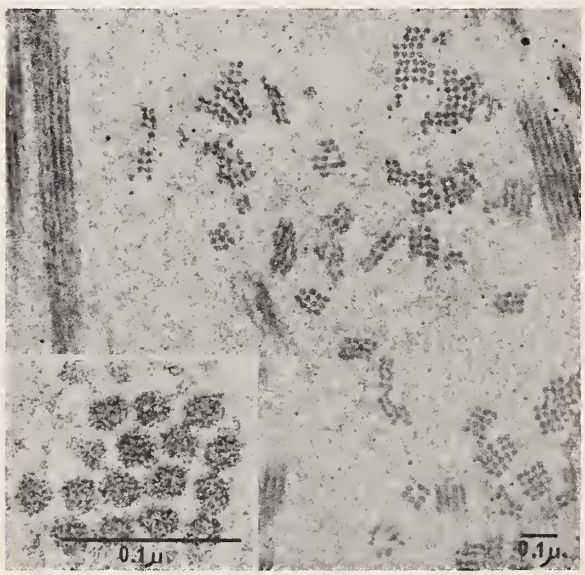


Figure 2.—Deoxygenated cell-free lysate from hemoglobin SS erythrocytes. Filaments lie parallel in bundles. No internal details (inset) are apparent. Transmission electron micrograph × 69,000, inset × 380,000. (From Bertles JF, Rabinowitz R, Döble J.[10] Reprinted with permission of the publisher, copyright 1970 by the American Association for the Advancement of Science.)

The pathophysiology of the cell with homozygous s hemoglobin is integrally related to its rigidity. It is crucial that the circulating red cell retain its deformability so that it does not inordinately increase whole blood viscosity and so that it can traverse the microcirculation where capillary diameters may be less than the diameter of the cell itself. There are two mechanisms by which a cell may become rigid: either by increased internal viscosity or by decreased membrane flexibility, or by both. Increased internal viscosity is certainly the initial event if not the most important, and probably only after prolonged or frequent alterations of the cell's internal milieu does the membrane abnormality begin to play a significant role, perhaps manifesting itself as the irreversibly sickled cell. Increased internal viscosity is a reflection of the severe molecular restraint that occurs within sickle hemoglobin during deoxygenation. The substitution of a valine for a glutamic acid in the sixth amino acid position of the beta chain imparts an abnormal conformational change during deoxygenation that leads to polymerization of the hemoglobin. This observation was initially made by Harris,[2] using hemolysates of sickle hemoglobin at low oxygen tensions. He observed that with stroma-free solutions containing hemoglobin s in concentrations similar to those found in the intact red cell, a semi-solid gel forms upon deoxygenation.

In Figure 1, under phase microscopy, from Harris' original work, we see small boat-shaped objects that polarize light and which are described as tactoids, nematic fluid crystals that form during deoxygenation. If one imagines these tactoids surrounded with a membrane we have a typical sickled cell.

Figure 2 is a transmission electron micrograph

of the cell free hemolysate demonstrating the rods of polymerized hemoglobin that form during deoxygenation. Here, some of the rods are seen longitudinally as parallel filaments and others are cut in cross section.

Figure 3 shows Murayama's[4] hypothetical model of hemoglobin s molecules during polymerization. Tetramers of hemoglobin consisting of α and β chains are stacked to form a single filament twisting in a helical fashion. Six hemoglobin filaments are postulated to twist around to form a cable with a hollow core. Subsequent workers, including Perutz,[5] have suggested that this mechanism is not completely plausible, but it serves a useful way of visualizing polymerization.

Figure 4 shows a scanning electron micrograph of sickle cells looking more like creatures at the bottom of the ocean. During the unsickling process, the hemoglobin in some of these spicules gets trapped and may just remain within the long filaments or may break off as small membrane covered hemoglobin spheres in the microcirculation.

Gelled deoxygenated hemoglobin s decreases the cell flexibility. As mentioned previously, cell flexibility or deformability is extremely important, because it enables blood to flow unimpeded; if rigid spheres were to replace red cells at the usual hematocrit levels, the resulting viscosity would be prohibitive to blood flow. The contribution of sickled cells to whole blood viscosity has always been deemed important.

Chart 1 shows the relationship between viscosity, hematocrit, and oxygen tension. With oxygenated hemoglobin s red cells, viscosity does not go up significantly. However, with deoxygenated sickled cells there is a dramatic increase in the viscosity of the whole blood, which varies directly with the hematocrit when the oxygen tension is zero. The significance of this increase in whole blood viscosity in the circulation may not be very applicable *in vivo,* since most patients with sickle cell disease have a hematocrit in the range of 25 percent. Even if all their cells were sickled, this would probably only equal the viscosity of normal blood at a hematocrit of 50 percent. The patient with sickle c (sc) disease, on the other hand, has an hematocrit approaching normal, and loss of red cell flexibility here significantly increases whole blood viscosity. More important is the increased internal viscosity of the individual cell itself. Capillary diameters are usually from 3 to 12 microns, which not only necessitates that red cells enter single file but that the cells deform in order to

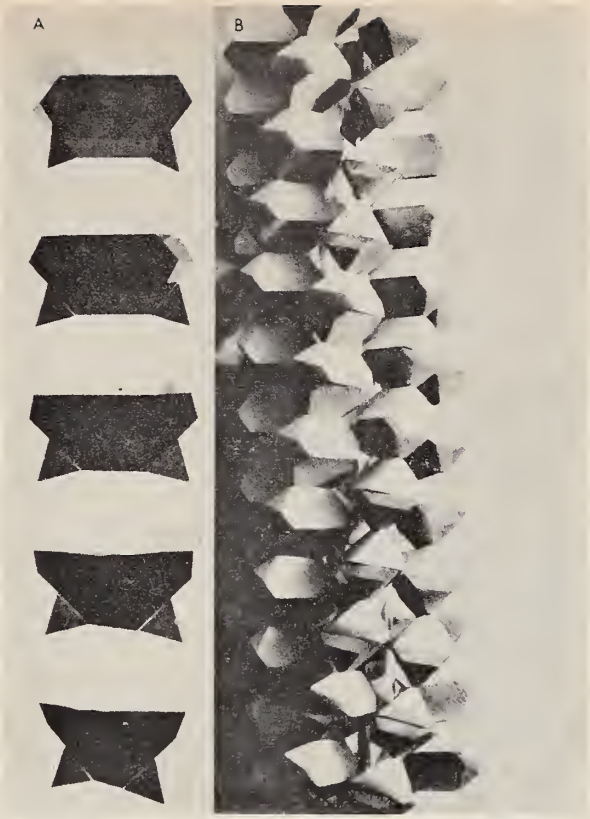


Figure 3.—A, five molecular models of hemoglobin S stacked to represent a segment of a monofilament. Each molecule consists of a pair of alpha chains (light tone) and a pair of beta chains (dark tone). **B,** six strands of hemoglobin S monofilaments twisted about a core to form a cable. (From Murayama M.[4] Reprinted with permission of the publisher.)



Figure 4.—Deoxygenated sickled cells. Scanning electron micrograph. (From Jensen WN, Lessin LS, Semin Hematol 7:421, 1970. Reprinted with permission of the publisher.)

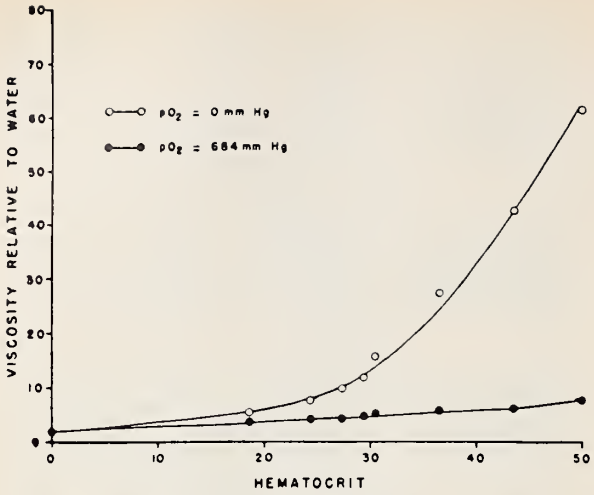


Chart 1.—The effect of oxygen tension upon the increase in viscosity that occurs with increase in the hematocrit of blood from a patient with sickle cell anemia. (From Greenberg MS, Kass EH, Castle WB, J Clin Invest 36:836, 1957. Reprinted with permission of the publisher.)

pass successfully through the venous side of the microcirculation.

One method of measuring red cell rigidity is to pass cells through a Millipore filter. In 1961 Jandl[6] demonstrated that Millipore filters with 5 micron pores allow normal red cells to pass through, but selectively retain sickle cells at oxygen tensions below 40 mm of mercury.

We became interested in just how rapidly this state of nonfilterability occurred following deoxygenation. We used an apparatus with two motor driven syringes, one containing a red cell suspension of the cells that were being tested and the other containing a dithionite solution, both leading to a mixing chamber which allowed rapid mixing and deoxygenation within 0.034 seconds. The Millipore filter was set at different time lapses from the mixing chamber. To our surprise, rigidity developed within 0.12 seconds after deoxygenation.[7] When cells were sampled from the segment of the tubing that corresponded to 0.12 seconds and immediately fixed, we found that they were morphologically normal. Yet, these very cells were too rigid to pass through Millipore filters, suggesting that a molecular interaction with a subsequent change in internal viscosity preceded shape deformity. It took another two seconds before the classical shape of the sickle cell developed.

When the reverse experiment was performed, using deoxygenated suspensions of sickle cells which initially were unable to pass through the filter, we discovered that within 0.12 seconds of reoxygenating them these cells regained their ability to pass through the filter. When we looked at these cells, we found that, at the time they could pass through the filter, most of them still had gross membrane distortion resembling holly leaf shapes. This suggests that during reoxygenation molecular reorganization precedes the deformability of the cell membrane—it took another four seconds before the cells had resumed their discoid shape. Hence, membrane distortion alone is not synonymous with rigidity of the cell.

For many years it has been known that deer erythrocytes can assume a sickled shape. Paradoxically, this occurs during oxygenation and not deoxygenation. Whitten[8] demonstrated that although this particular deformity is somewhat analogous to sickle cells in humans, there is neither tactoid formation nor pronounced increase in viscosity even with 100 percent of deer sickling. Moreover, the abnormal shape of these cells apparently does not lead to intravascular thrombosis in deers.

When our filtration studies were applied to other sickle hemoglobinopathies, we found that homozygous s and s-thalassemia (where the concentration of s hemoglobin was equivalent to that in the homozygous s patients) were similar in that after 0.12 seconds almost no cells passed through the filter. sc cells, on the other hand, demonstrated no decrease in filtration until 0.5 seconds had elapsed. Sickle trait red cells, as well as normal cells, showed no change in filterability after four seconds, which was the maximum time in our system.

Hemoglobin s is well known to undergo molecular interaction with other hemoglobins during deoxygenation. If non-s hemoglobin served only as an inert diluent in hemoglobin mixtures, the mean hemoglobin s concentration would be a measure of the tendency of red cells to sickle. However, this is not the case in hetcrozygotes. Certain interacting hemoglobins lower the critical content of deoxygenated hemoglobin s necessary to induce red cell sickling or gelling of hemoglobin solutions. Both the magnitude and the strength of these interactions may be determined by measuring the minimum concentration of hemoglobin re-

quired for tactoid formation. In this way, it has been observed that hemoglobin D, C, and A react in that particular order with hemoglobin S during deoxygenation.[9]

Bertles[10] has recently demonstrated that hemoglobin C or A can join with hemoglobin S to form hemoglobin filaments during deoxygenation which are absolutely indistinguishable from those which we saw previously in the electron micrograph of hemoglobin S alone. Hemoglobin F does not enter into this relationship. If there is a significant degree of interaction, the clinical state of a patient is affected despite levels of hemoglobin S in the red cell approximating those found in sickle trait which is usually 40 percent of the total hemoglobin. Thus, patients with hemoglobin SD can be just as incapacitated as those with homozygous S disease. At the other extreme, hemoglobin F shows negligible interaction and patients with 70 percent hemoglobin S and 30 percent hemoglobin F distributed in their cells homogeneously have a benign course.

These interactions are related to complementary sites of binding about which we know very little. Although there can be significant interactions between S and C, a lower oxygen tension is required to initiate sickling in S and C cells. With oxygen tensions of approximately 60 mm of mercury, we begin to see sickling in patients with homozygous S disease. At the other end of the spectrum, the sickle trait requires oxygen tensions of 15 mm of mercury to initiate sickling; in between is SC disease which requires an oxygen tension of about 30 mm of mercury. Hence, most patients with SC disease have few sickle cells in their peripheral blood, and have little or no anemia. Nevertheless, they have certain clinical manifestations attributable to vascular occlusions that are even more common than in homozygous S disease. In other words, patients with SC disease are noted to have aseptic necrosis of the capital epiphysis of the humerus and femur, and small vessel occlusions in the periphery of the retina that may lead to retinitis proliferans and detachment, with bleeding into the vitreous. In fact, these patients may present for the first time with sudden loss of vision.

No one is certain why these events occur, but there are plausible speculations. First, the initial lesion seems to occur in terminal vessels where the oxygen content is low and the collateral circulation poor. The blood supply both to the end of the femur as well as to the periphery of the retina is an end-arterial system without anastomoses which predisposes to hypoxia and tissue damage once blockage occurs. Second, many patients with SC disease have a normal hematocrit. The patient presented here this morning was more or less in the intermediate range, having a hematocrit of about 35 percent. Any noxious environment that could initiate sickling will result in a much greater increase in whole blood viscosity if the hematocrit approaches normal. Thus, if we have a patient with SC disease who develops sickling with a normal hematocrit, the increase in blood viscosity is almost four times as great as might occur with a hematocrit of 25 percent. This is analogous to the whole blood viscosity in a patient with a hematocrit of approximately 90 percent. An additional cause of hindrance to blood flow may be that sickle cells with SC hemoglobin have a peculiar internal structure, which leads to more difficulty in negotiating narrow and tortuous capillaries than the homozygous S cell.

It has been shown by high speed ciné[11] that the normal red cell undergoes considerable bending and develops a parachute shape on entering capillaries. The sickle cell is incapable of this, but sickle cells do align their axes in the direction of flow and proceed head to tail through narrow capillaries;[12] they have the greatest difficulty at points of bifurcation since they are no longer capable of bending. Diggs[13] noted peculiar crystal shapes in SC cells and this may further hinder individual red cell flow through capillaries even at normal oxygen tensions. Since not all the hemoglobin C may polymerize with hemoglobin S, it is possible that free hemoglobin C may undergo crystal formation. Charache[14] and others have demonstrated that homozygous C disease has an increased internal viscosity and that intraerythrocytic crystals form under conditions that dehydrate the cell, increasing the mean hemoglobin concentration. Tosteson[15] and more recently Mentzer[16] demonstrated pronounced loss of potassium during sickling, and this may lead to further cell dehydration and initiate hemoglobin C crystallization.

The major factor in the initiation of sickling is oxygen tension. Patients with sickle hemoglobinopathies breathing inspired air with low oxygen tension (half that of normal air) for a half hour develop a very high percentage of sickling without pain crises.[17] Alhough oxygen unsaturation *per se* causes a predictable increase in the number of sickle cells, other factors may be needed *in vivo*

to initiate significant rheologic changes and thrombosis *in situ*. It is well known that pH alone influences the percent of sickling and that sickling begins at a much higher oxygen tension if the pH is lowered. In other words, at an oxygen partial pressure (pO_2) of approximately 75 mm of mercury we already begin to see sickling when the pH is lowered to 6.86. By contrast, if the pH is elevated to 7.53, sickling is prevented until lower oxygen tensions are reached. These phenomena are due respectively to a shift of the oxygen dissociation curve to the right with a decrease in pH and a shift to the left with an increase in pH (Bohr effect).

Certain tissues appear to be predisposed to infarction. Most notable is the spleen, where some red cells pass through apertures as small as 0.5 micron in the basement membrane separating the cord and the vascular sinus. Here, the cells are also subject to decreased pH, stasis, and glucose deprivation. As a result, most homozygous s patients have a shrunken fibrotic spleen by the time they reach adolescencc. Moreover, young children can have a reversible functional asplenia.[19] The kidney is also quite vulnerable, particularly the renal medulla, where blood in the vasa rectae is hyperosmolar. Necropsy studies have shown that the vasa rectae of adults with sickle cell disease are completely destroyed.[20] As a clinical corollary, most homozygous s patients over the age of ten years can no longer concentrate their urine above 400 to 450 mOsm per liter. *In vitro* studies have shown that hypertonic salt solutions above 600 mOsm per liter can initiate sickling.[21]

I would now like to briefly discuss the irreversibly sickled cell. These cells can be produced by sterile anaerobic incubation for 24 hours, and can also be produced by four or five sickle-unsickle cycles in a single cell preparation. These cells are distinctive by electron microscopy, even when oxygenated. There are no hemoglobin filaments, and the serrated margins obscure membrane details. When deoxygenated, there is much closer packing of the hemoglobin filaments with a central bundle in the long axis of the cell. These cells have greater osmotic and mechanical fragility, greater internal viscosity, less deformability when oxygenated, and pack at the bottom of the tube during ultracentrifugation. Some rather exciting preliminary studies done at the University of California indicate that the membrane in these cells is deficient in lipid, especially when deprived of adenosine triphosphate (ATP).[22]

Treatment

Let us now turn to the treatment of this disorder. Many types of therapy have been tried but have not proved to be very effective. Transfusion, however, remains helpful. If we transfuse enough to reach an hematocrit of about 35 percent, we can completely shut off the patient's own marrow red cell production and he will stop making sickle cells. If done repeatedly, however, this creates obvious problems. It has been shown that we might be able to benefit the patient by doing exchange transfusions so that his blood contains about 30 percent normal cells and 70 percent hemoglobin s cells.[23] This creates a situation *in vitro* where much lower oxygen tensions are required to achieve a significant increase in viscosity. Modifying the hemoglobin molecule by either blocking the binding sites or by chanigng the oxygen affinity of hemoglobin s are potentially hopeful approaches. Urea interrupts hydrophobic bonding, and some workers claim that the use of urea may completely abort sickle crises.[24] There is no doubt that in the test tube urea can prevent sickling, the increase in whole blood viscosity, and the other changes associated with sickling. However, a very high concentration of urca is required, comparable to a blood urea nitrogen (BUN) of about 560 mg per 100 ml.[25]

Cyanate would seem to have much more potential as a therapeutic agent. Studies from Rockefeller University[26] have shown that cyanate carbamylates the N-terminal amino group of the alpha and beta chains of hemoglobin. This protects the red cells from sickling at low oxygen tensions. In addition to blocking the binding sites of hemoglobin s interaction, there is a significant shift in the oxygen dissociation curve to the left so that hemoglobin s has an increased affinity for oxygen which may have a protective effect. Hemoglobin s cells that have been incubated with cyanate and tagged with 51-Cr have a much longer survival time in the circulation than sickle cells without cyanate.[27] At first glance this is rather encouraging; however, there are potential problems. One of the most important is what cyanate will do to other proteins in the tissues, for we

do know that cyanate binds to them also. Another problem is that we now have created a patient who has homozygous s cells which are increasing in the circulation, but whose cells are still amenable to sickling and viscosity changes, but at a lower oxygen tension. We may be creating a patient with the same problem as our patients with sc disease. His hematocrit may approach normal, but in a very noxious environment he may still experience sickling and thrombosis.

By these attempts to affect intermolecular binding, we have come full circle again since Pauling's initial discovery of this molecular disorder. It has become increasingly clear that more than one amino acid substitution will be necessary to explain the variable clinical expression we are beginning to see even in patients who appear only to have homozygous s disease. Reports of patients in their forties, fifties and even sixties suggest that a search for additional modifying factors must be undertaken, especially with respect to other silent hemoglobin mutations or variants in glycolytic enzymes that may be involved in preservation of membrane integrity. The massive screening of patients now in progress may enable us to define better the various clinical spectra and find genetic and environmental explanations for them.

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EDITORIAL

Toward Unity and Renewal

THESE ARE TIMES of pressing need for both unity and renewal within the medical profession. The pressures for greater unity are considerable in the face of an increasingly difficult and often hostile practice environment that seems bent upon attacking, exploiting and even discriminating unfairly against a profession which seeks to serve those who are ill and improve the health of those who are not. The pressures for renewal are just as real and come from leaders within the profession and also reflect the attitudes and energy of a substantial number of younger physicians, interns and residents, and medical students.

There are many signs of growing health and vigor. During the past year many state medical associations (including the CMA) have increased their membership. There is evidence of closer day-to-day coordination at the county, state and national levels of organized medicine, and of increasing participation and involvement by younger physicians, physicians in training and physicians-to-be, in the affairs of the profession. Much of this change had its early development through the work of the California Medical Association.

At its meeting just concluded, the House of Delegates took an important further step toward unity and renewal for the medical profession in California. It voted to admit interns, residents and medical students of the state to meaningful membership in the CMA and to give their elected representation full participation in the deliberations and actions of the House. It is too early to predict what the long-range effect of this will be, but one senses that this action marks some kind of turning point in the history of the association, and that there is every reason to believe that it will not only strengthen the association but will also lead to better health care for all Californians. The House is to be congratulated.

—MSMW

Physician Involvement in Health Care Planning

ANY COMPLEX UNDERTAKING requires careful and realistic planning if it is to be successful, and health care in this nation is without question a complex undertaking. Complexity is to be found in the financing, in manpower development, in assessment of quality and cost benefits of medical and health care services, in the operation of facilities, and more often than not in the care of a single patient. This complexity is a function of the interdependence of many different and to a considerable extent independent components. What affects one inevitably affects many others. Efforts to introduce rational planning into this complex undertaking have been under way for some time, but they have not been very successful. Yet the need for planning persists. In fact it becomes more pressing each day.

To accomplish anything at all, planning must result in action. The action must be carried out by the actors, the doers. Too often in health care, the planning and the action have been separated, and particularly those who are most affected by the plans and those who are expected to carry them out have been left out of the planning process. These are the consumers and providers, to use health care jargon, or patients, practicing physicians and other allied professionals, to use medical jargon. The result has been that these often do not have much interest in carrying out a plan or plans which they do not understand and which may or may not be responsive to their needs or capabilities.

Recently there has been a concerted effort by government to assure consumer and patient involvement in planning for health and medical care. By law, consumers dominate the comprehensive health planning councils, and recent court decisions on informed consent will make the patient a full participant in planning his own medical care. But there has been a curious omission of any similar effort on a similar scale to involve the health care field, the professionals and others who are expected to carry out the plans. The result

has been much sterile or unrealistic planning with enormous waste of human and fiscal resources.

It is time that the inherent complexity of the health care undertaking and the resulting need for realistic planning be recognized by all concerned. This is just as true for the complex problems of health care delivery as it is for the care of a patient with a complex illness. The role of the consumer and the patient has now been given recognition perhaps even beyond its due. The role of the practicing physician in planning for health care delivery has yet to be fully acknowledged either by the practicing profession or by the planners in government or elsewhere.

Along with many others, practicing physicians and the medical profession as a whole have been slow to recognize the complexity of the health care undertaking, the interdependence of its many and varied components, and the need for realistic planning if so complex an undertaking is to function smoothly, effectively, efficiently and to the reasonable satisfaction of all concerned. Planners, particularly those in ivory towers and in government, have been slow to recognize that the best laid plans, even when backed by the force of law, will go awry if they are unrealistic or impracticable, or if physicians and other providers of medical and health care services do not understand the plans or have little or no incentive to make them work.

What is clearly needed is more recognition that realistic health care planning is essential, and that those who plan and those who will carry out the plans should be more nearly one and the same. More direct physician involvement should be a primary goal of the medical profession and the society it serves.

—MSMW

Tumors of the Heart

AMONG THE RARER FORMS of cardiac disease, tumors of the heart are playing an increasingly important role. Once only a pathological curiosity, cardiac neoplasms can now be diagnosed with reasonable accuracy. In this issue, two articles deal with the opposite ends of the spectrum of cardiac tumors: Dr. Laws and his associates[1] report five cases of primary malignant tumors of the heart; Dr. Comer and his colleagues[2] review briefly the subject of left atrial myxoma. The former deals with rapidly progressive, usually incurable neoplasms; the latter with one of the few curable forms of cardiac disease.

The emphasis of the paper by Laws et al is on the radiographic features of primary malignant cardiac tumors. The authors provide important clues that can alert the clinician to the possibility of an unusual form of heart disease and suggest the possibility of a cardiac tumor. Most primary malignant tumors are invasive and involve extracardiac as well as intracavitary structures. Exploratory operations are almost always necessary, inasmuch as the nature of the tumor and its incurability cannot, as a rule, be predicted from the clinical findings.

In clinical importance, however, primary malignant tumors cannot match benign cardiac tumors, particularly myxomas of the heart, which present an important diagnostic challenge in today's cardiology.

The question of how rare are cardiac myxomas cannot be answered with any degree of accuracy, but it is estimated that in an active department of cardiology one can expect at least one case of cardiac myxoma a year. The figure of 87 successfully removed left atrial myxomas quoted by Comer et al may be misleading; this lesion is no longer considered rare enough to justify the reporting of individual cases or series of cases routinely, so that only those with unusual aspects are likely to appear in the literature.

As is pointed out by Comer et al, the consequences of left atrial myxoma—and myxomas in other locations as well—fall into three categories: (1) mechanical consequences of the tumor, (2) embolic manifestations, and (3) systemic reactions. The mechanical effects involve interference with the flow of blood, usually in the form of obstruction or valvular incompetence; systemic embolization occurs in left-sided lesions and pulmonary embolization in right-sided tumors. Major emboli in peripheral arteries may require embolectomy, and examination of the extracted embolic material may establish the diagnosis of myxoma. Systemic constitutional reactions include fever, anemia, weight loss, malaise, elevated sedimentation rate, and the presence of abnormal serum proteins. These manifestations have never been

adequately explained; they may be due to microembolization or to immune reactions.

As a result of these manifestations, the clinical picture of cardiac myxomas varies greatly.[3] Its most common form—left atrial myxoma—masquerades, in the great majority of cases, as mitral valve disease. Left ventricular myxoma may show features suggestive of hypertrophic subaortic stenosis; right ventricular myxoma may suggest right ventricular outflow obstruction; right atrial myxoma may imitate tricuspid disease or may even cause right-to-left shunts resembling cyanotic forms of congenital heart disease.[4] When the size of the myxoma or its location are insufficient to produce clear-cut features of mechanical interference with blood flow, the clinical manifestations may be more subtle. Unexplained cardiac failure suggestive of cardiomyopathy may develop as a result of cardiac myxoma; embolic phenomena without any evidence of cardiac disease have been reported. A generalized systemic disease may ensue due to the constitutional manifestations of the myxoma; if cardiac murmurs are also present, the clinical picture may suggest the diagnosis of infective endocarditis or acute rheumatic fever.

The clinical course of cardiac myxomas is as variable as the clinical manifestations. Both in duration of the symptoms and signs and in the order in which they appear, there is a wide range. Mechanical manifestations may be present with little change for months or years in some patients, or may progress rapidly in others. The systemic manifestations may appear early or late, or be absent altogether. As a rule, surgical removal of the tumor cures the disease and reverses all the secondary manifestations (except the possible permanent damage produced by emboli). However, occasionally irreversible damage may result, as exemplified by two young patients[3] who died at variable time intervals after successful complete removal of the tumor. In one, intractable cardiac failure persisted after the operation; necropsy revealed changes in the cardiac muscle resembling those of myocarditis.

The diagnosis of cardiac myxoma is based on the recognition of clinical symptoms and signs on noninvasive screening tests and angiocardiographic demonstration of the myxoma. Many clinical features have been frequently cited as suggestive of cardiac myxoma; among these are: syncope, particularly related to body position; positional change in murmurs; early diastolic sounds ("tumor plop"); the sudden onset and rapid progression of signs of valvular disease. However, the sensitivity and specificity of these clinical findings are of a low order; their presence can, at best, vaguely suggest the possibility of a cardiac tumor. The most important diagnostic noninvasive tool is echocardiography. Myxoma, a pedunculated tumor, has sufficient motion to give a characteristic echo, which is unlikely to be confused with that of other space-occupying, intracavitary structures such as solid tumors or thrombi.

Selective angiocardiography permits, in almost all cases, a definitive diagnosis, outlining the size, shape, and mobility of the tumor.

Various problems related to the surgical treatment of myxoma are discussed by Comer et al. However, they are overshadowed by the importance of early recognition. The clinician's acumen in initiating the tests that establish the diagnosis of myxoma involves a high index of suspicion. Every patient with unusual signs of mitral valve disease is a suspect for the presence of a cardiac tumor. All conditions that do not fit in the common diagnostic categories, all patients with infective endocarditis and negative blood cultures, or with unexplained febrile episodes should be screened for the possibility of cardiac tumors. The ease with which echocardiography can now be performed and the available facilities for cardiac catheterization and angiocardiography make it also advisable to screen and then to study patients with the typical picture of mitral valve disease for the remote possibility of cardiac tumors. Surgical treatment for myxoma is indicated earlier than for rheumatic heart disease, and the specter of irreversible cardiac damage and disabling systemic emboli makes early diagnosis of great importance.

The great majority of cardiac diseases involve life-long chronic afflictions. The drama of surgical relief for some of them has generated boundless enthusiasm, yet, only very few operations completely cure cardiac disease. Cardiac myxoma is one of such lesions and, thus, presents a great challenge to the cardiologist and surgeon alike.

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Childhood Autism

INFANTILE AUTISM, first described in medical literature just three decades ago,[1,2] is a serious psychiatric disturbance of childhood which dooms a majority of its victims to lifetime disability. Early in life these children have distorted relationships with their parents. The term *autism* (Greek for "self-ism") refers to their self-absorption and withdrawal from social transactions. Some such children remain totally mute while others fail to develop communicative speech. Stereotyped mannerisms and obsessive insistence on the preservation of sameness are other characteristics.[1,2]

Autism has become almost a household term as a result of widespread publicity in the lay press. The timely appearance of a scholarly review of childhood autism in this issue of CALIFORNIA MEDICINE provides physicians with an opportunity to become cognizant of this subject in order to give knowledgeable answers to the questions raised by their patients. Among such interested patients are concerned parents who have observed their own children exhibiting symptoms associated with autism as reported in newspaper articles and the *Ladies' Home Journal*. Other parents have become alarmed because their children have been actually classified as autistic at school or elsewhere. The word *autistic* has been so loosely applied that children so labeled range over a broad clinical continuum from those who are in fact severely handicapped with early infantile autism as described by Kanner to essentially well functioning children who are merely less outgoing and less gregarious than their peers.

Autism has been well described as a concept that has been engulfed in a morass of semantic confusion.[3] Dr. Ornitz has performed a useful service in clarifying some of the diagnostic turbidity involved in the use of such overlapping diagnostic terms as early infantile autism, childhood schizophrenia, childhood psychosis, early-onset psychosis, atypical development, pseudo-mental deficiency and so forth as they are applied to the diagnostic spectrum of severe emotional, behavioral and thought disorders of childhood. In spite of a clinician's best efforts to be precise in using such diagnostic descriptions, many individual patients do not quite fit into the diagnostic pigeonholes and some even move from one diagnostic category to another with the passage of time. Happily, a few even approach normality in the course of therapy. Most such children in this country are officially diagnosed as having childhood schizophrenia because the official diagnostic handbook of the American Psychiatric Association provides for no other appropriate subclassification.[4]

Since symptoms vary with age, the detailed systematic review of typical clinical signs of autism at sequential stages of childhood development has practical applications for all clinicians who encounter disturbed children in their practices. The discussion of differential diagnosis will also prove useful. Infantile autism and other psychotic disorders are not so rare in childhood as was previously supposed. The prevalence of childhood schizophrenia is between 4.5 and 3.1 per 10,000, including a prevalence of infantile autism between 2.1 and 0.7 in the best available British and United States statistics.[5] Often the condition has gone unrecognized or misdiagnosed. It is also unfortunately true that parents of such children are still occasionally reassured with "Don't worry, your child will probably outgrow it." This is unfortunate, for there is evidence that early intervention with intensive treatment can increase the child's chances of avoiding spending his lifetime in institutions.

Evidence that intensive psychiatric treatment can improve the autistic child's prognosis was an important fact which was either overlooked or disregarded by Dr. Ornitz in one of the references he cited.[6] Further evidence of the beneficial effects of psychotherapeutic work appears in another major long-term follow-up report, which was in press and thus not available to the reviewer.[7] While it is, of course, impossible to cover everything in such a review, this particular information is of such practical and humanitarian importance that it must be called to the attention of the reader. This can be done most concisely by a table showing the long-term outcome of the major long-term follow-up studies. Because of differences in diagnostic criteria and evaluation methods, results can-

not be considered exactly comparable, but it is a striking fact that the two series showing the best outcome were the only ones in which all the children received intensive residential milieu treatment in psychotherapy-oriented institutions. In Bettelheim's series the children were treated separately from the parents although some parents obtained psychoanalytic treatment on their own.[6] In Szurek's series there was continued contact between children and their parents (most children spending week-ends at home) while the children received residential milieu therapy and psychotherapy and all parents received concomitant individual psychotherapy as well as conjoint therapy, group therapy, demonstration, and consultation.[7] It seems significant that there was no provision of psychotherapeutic treatment of comparable consistency and intensity in the other series reported.[8-12] The criteria for the best outcome group varied in each series but implied essentially self-dependent functioning outside an institutional setting either gainfully employed or attending school at an age-appropriate level.

A Comparison of Follow-up Studies

Study	Total Sample	Best Outcome Group	
		Number	Percent
Eisenberg[8]	64	3	5
Bender[9]	50	5	10
Kanner[10]*	96	11	11
Creak[11]	100	17	17
Rutter[12]	63	11	17
Etemad and Szurek[7]	84	24	29
Bettelheim[6]	40	17	42

*Includes cases reported by Eisenberg above.

Adapted from: Etemad J, Szurek SA: A modified follow-up study of a group of psychotic children. *In* Szurek, SA, Berlin IN (Eds): Clinical Studies of Childhood Psychoses. New York. Brunner/Mazel. In press.

Autism has been described as a disorder whose cause is unknown and whose treatment remains uncertain.[13] There are no shortages of theories and treatment methods, however. Theories of cause include the following models: autism as social withdrawal, introversion, a type of schizophrenia, a psychogenic disorder, a deprivation syndrome, a genetic disorder, a type of subnormality, a cognitive/language disorder, or a developmental disorder.[14] "Nearly equal groups of authors favor one of the following three theoretical approaches: Nonorganic, organic-environmental, and organic," was the conclusion of a recent review of all 90 papers on etiology that were found in three annotated bibliographies.[16-18] Most psychiatric conditions are multidetermined and perhaps the actual situation of childhood autism is appropriately covered by the words of John Romano, who, in speaking generally of psychiatric disorders, said, "I know of no cases which had exclusively single cause determinants, whether they be solely biologic, or genetic, psychologic, or social."[19]

Kanner considered infantile autism to be an inborn disorder, but no anatomical or biochemical findings have yet been discovered in spite of diligent search. Although Kanner found it impossible to believe that the specific personality traits he observed in parents could influence infants so early in life, recent precise observations of young infants[20,21] and research on infant monkeys[22] have shown evidence of profound and lasting effects from disturbances in the mother-child relationship shortly after birth. One of the most active researchers with infant monkeys has pointed out an uncanny similarity between the state of infant monkeys reared in social isolation and the clinical observation of autistic children.[22] Harlow postulates that autism may be the result of coldness, ambivalence, double-binding messages, and lack of physical contact by a caring object, just as social isolation produces a similar state in infant monkeys.[22] A mother of an autistic child made the following observation: "What seems impaired is not only the capacity for affect, but another capacity perhaps even more fundamental, the capacity for undertaking exploratory behavior and sustaining it."[23] Aversion for exploration is another manifestation of the urge for the "preservation of sameness" as described by Kanner. It is likewise a characteristic of socially isolated primates.[22]

In Kanner's classical textbook, *Child Psychiatry,*[24] early infantile autism is discussed in a section of the chapter on childhood schizophrenia. It seems appropriate to conclude this discussion with some words from the concluding paragraphs of that chapter by Kanner, who first recognized and described early infantile autism:

> Even if the role of heredity and constitution in the production of schizophrenic behavior were known exactly, there is nothing that can be done about them. . . . Drugs proved of little, if any, value as remedial agents. The shock therapies disappointed those who tried them with children.
>
> Greater reliance is to be placed on people and their attitudes as remedial agents. Change of environment means a change of people. Its effect depends on the attitudes of these people. Whenever possible, frequent sessions with a psychiatrist may enhance the child's ability to

form relationships and wean him away from the temptation to schizophrenic withdrawal.

Treatment of childhood schizophrenia is still in the stage of experimentation. But definite trends have emerged which no longer justify an attitude of therapeutic nihilism. . . .

The present author agrees wholeheartedly with these words. There is hope for autistic children with continued research and further development of psychiatric treatment methods.

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California's Shame—The Fluoridation Issue

IT IS NOW 30 YEARS since the relationship of fluoride ion in drinking water to dental caries was first observed and more than 15 years since controlled water fluoridation was demonstrated to be effective and safe.[1,2] By 1970, approximately 60 percent of all Americans using public water supplies were receiving sufficient natural or supplemental fluorides from this source. In nine states 90 percent or more of the population served by public water supplies receive supplemental fluorides. In Connecticut, the legislature decreed in 1965 that all public water supplies serving more than 20,000 persons must control their fluoride ion content at a level suitable to insure maximum caries prevention. Despite the foregoing, California, the most populous and perhaps richest state, provides only 18 percent of its population served by public water supplies with sufficient fluoride either natural or supplemental to insure the development of normal tooth enamel. Included in this 18 percent are more than 50 communities or water systems with a population close to one million where natural fluoride content was sufficient to provide adequate nutritional levels. As of 1 January 1972, only five water systems in California serving populations over 100,000 provided their customers with controlled fluoridation. These systems were: Alameda County Water District, Contra Costa County Water District, Long Beach, San Francisco, and Vallejo.

The consequences of this deplorable situation are, of course, inflicted principally on those whose teeth are in the developmental stage, the children and future adults of this state. They are destined to suffer a huge burden of preventable disease in the form of dental caries and tooth loss. Furthermore, as so often happens, it is the poor and the ethnic minorities who suffer disproportionately since they have neither access to care facilities nor financial resources to remedy the effects of this deprivation.

What explains the situation in California? It

would appear to be due in large part to the practice of making the decision as to whether or not to fluoridate dependent on public referenda.[3] This, in a sense, "legitimizes" the controversy and implies a relative equality between pro and con arguments. The result has been that almost three-quarters of the attempted referenda have failed. There is no reason this technical issue needs to be decided by public vote. Judicial tests have established that fluoridation is not an abuse of the states' police power, does not violate guarantees of due process or equal protection under the law, is not an unconstitutional limitation on freedom of religion, and does not contravene state pure food and drug laws. Moreover, these tests confirm that a state may delegate to local agencies the authority to fluoridate public water supplies. In over 70 percent of the more than 5,000 communities in the United States where controlled fluoridation is practiced, the decision was made by the governing body alone.

In 1971 the California Legislature passed legislation which provided that both public and private elementary and secondary schoolchildren should be offered an opportunity to receive topical application of fluoride annually. Even this quite inadequate approach was nullified in 1972 when the legislature suspended implementation until the United States Food and Drug Administration approves a fluoride preparation for such use. Of course, topical application in private practice and in public health programs has been standard practice for about 20 years throughout this country.

Fluoridation of public water supplies is an effective, safe and inexpensive method of reducing dental caries by about 60 percent and tooth loss by a substantial amount. Medical and dental practitioners, public health officials, and responsible elective officeholders in the state of California should reconsider their positions with respect to this important issue and be sure that their actions are consistent with the ethics of their professions and the responsibilities of their offices.

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CASE REPORTS

Refer to: Kaufman SL, Frederickson R: Thyroid-binding globulin deficiency in a patient with Beckwith's syndrome. Calif. Med 118:63-66, Apr 1973

Thyroid-Binding Globulin Deficiency in a Patient with Beckwith's Syndrome

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THYROID-BINDING GLOBULIN (TBG) deficiency has infrequently been reported in medical literature. In the infant described here, it is associated with Beckwith's syndrome[1] (macroglossia, omphalocele, and macrosomia) and inability to taste phenylthiocarbamide (PTC). The association of these three abnormalities has not been recorded previously. The clinical picture may be difficult to distinguish from that of hypothyroidism.

Report of a Case

The patient, now two years old, is a Pakistani boy in good health with no symptoms of hypothyroidism or hypoglycemia. His growth velocity has exceeded the expected rate (Chart 1); his height is 97 cm (+3.6 S.D.), weight 14.5 kg (+1 S.D.), head circumference 51 cm (+2 S.D.). A fading flame nevus on the forehead extends to the upper eyelids. There are small horizontal notches on the pinnal lobes. The abdomen has a well-healed scar from repair of an omphalocele. Liver and spleen are of normal size. Motor and intellectual development are appropriate for age. His appearance at three months is shown in Figure 1, at 12 months in Figure 2.

He was born at term to a gravida IV, para 4, 34-year-old woman whose pregnancy was associated with dry skin, constipation, and a weight gain of 13.6 kg. At birth, the infant weighed 3.6 kg and was 53.3 cm long; head circumference was 35.6 cm. A 6×6-cm omphalocele was present, and macroglossia was evident. There were flame nevi on the nape and both eyelids. The testes were not palpable. The umbilical cord contained three blood vessels.

The first stage of omphalocele repair was carried out when the patient was two hours old. At 48 hours, findings on complete blood count and urine analysis were normal; serum calcium was 9.1 mg, potassium 6.6 mg and chloride, 109 mg per 100 ml. Carbon dioxide combining power was 22.5 mEq per liter and glucose content was 60 mg per 100 ml. Electrophoresis showed normal serum protein. Maximum total bilirubin, reached on the fourth day of life, was 13.6 mg per 100 ml.

By age 21 days, macroglossia had increased, constipation had developed, and the spleen tip had become palpable; the testes had descended.

At six weeks of age, both the distal femoral and proximal fibular epiphyses were demonstrated on bone age roentgenograms. The serum thyroxine level was 1.4 μg per 100 ml (normal 3.5 to 6.5). The administration of desiccated thyroid was started at 15 mg daily and was gradually increased to 45 mg daily, where it was maintained for four months. The serum thyroxine level did not rise, and the macroglossia was not reduced. Neither the infant nor his mother was known to have ingested any drug associated with distortion of the serum thyroxine level or of thyroid function.

The growth rate continued to be exceptionally rapid, without development of hepatosplenomegaly. At five months, the second stage of omphalocele repair was accomplished. At nine months, abrupt withdrawal of thyroid therapy did not alter the growth rate and was not followed by the development of clinical hypothyroidism. At this time, peculiar notching of the earlobes was first noted.

At age 14 months, the infant was admitted to the hospital for evaluation of glucose homeostasis and growth hormone levels. At no time had there

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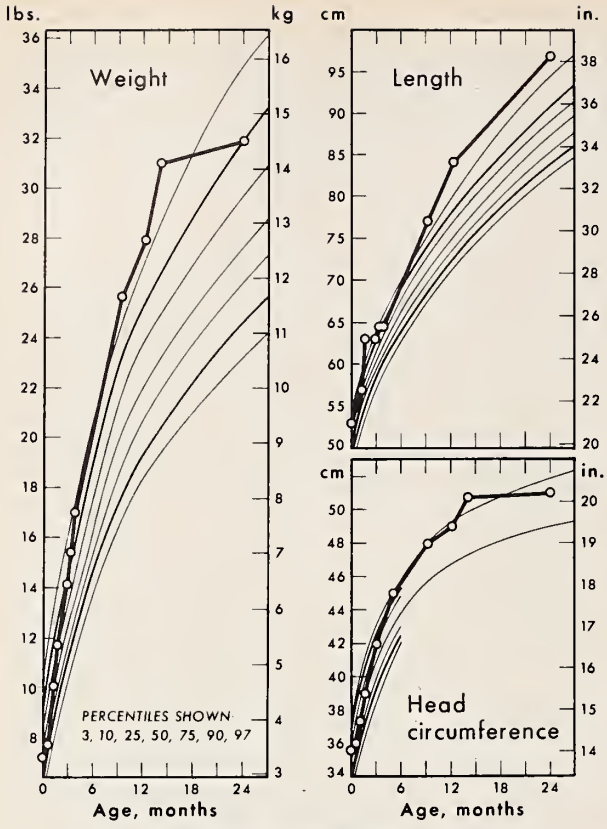


Chart 1.—Rate of growth of proband.

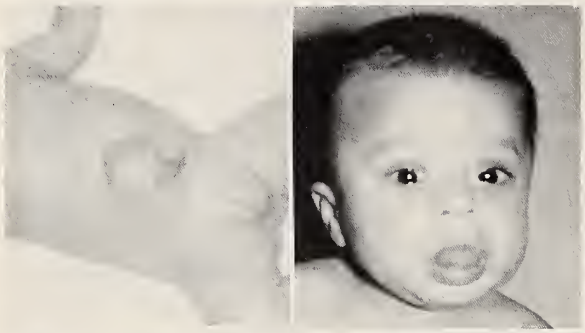


Figure 1.—Infant at three months. Note partially repaired omphalocele, large tongue, and flame nevus of forehead.

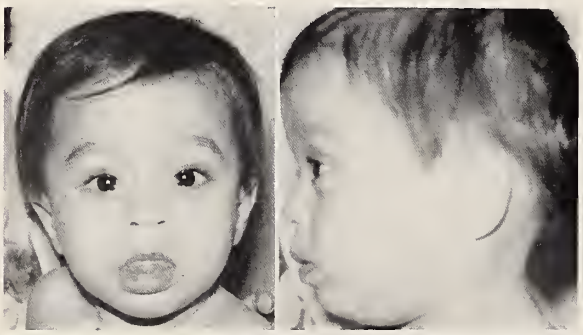


Figure 2.—Infant at 12 months. Note large tongue, flame nevus still present, and notching of earlobes.

been symptoms referable to hypoglycemia. Responses to the following studies were normal: Six-hour glucose tolerance test, insulin tolerance test, human growth hormone response during the insulin tolerance test (9.8 nanograms at 90 minutes), and serum cortisol (30.8 μg per 100 ml during fasting, with no rise during hypoglycemia). See Table 1.

Moderately short stature is characteristic of this child's paternal and maternal families. Diabetes was recognized in a paternal grandfather at age 50. Thyroid studies of the infant's parents and his two siblings (Table 2) demonstrated partial deficiency of TBG in the infant, his mother and his only sister. All family members tested were unable to taste PTC.

Discussion

Beckwith's syndrome may be confused with hypothyroidism in any case. In this infant, two associated disorders contributed to the difficulty in distinguishing these two entities: (1) The infant, his mother and his sister had partial deficiency of thyroxine-binding globulin; (2) all tested members of the family were PTC nontasters. PTC nontasting has been seen in familial hypothyroidism, apparently as an inherited characteristic.[2-4] The significance of the latter finding in this family is unknown.

Since Beckwith's first described macroglossia, omphalocele, and macrosomia as a syndrome, about 50 additional cases have been reported and additional features have been observed, including hypoglycemia, flame nevi of the head and neck, and peculiar notching of the ear.[5] Some of these features are similar to characteristics of hypothyroidism, but they are not identical. The macroglossia of cretinism recedes during therapy and remains unchanged in Beckwith's syndrome. The umbilical hernia of cretinism is unrelated to the omphalocele of Beckwith's syndrome. The lethargy of cretinism reflects low metabolic functioning; the lethargy of some infants with Beckwith's syndrome is due to hypoglycemia. The infant reported here was not lethargic.

Several aspects of the disorder in this infant, and various findings in his family, suggested hypothyroidism. These include the mother's weight gain, constipation, and dryness of skin during pregnancy; and her serum thyroxine level of 2.9 μg per 100 ml seemed to confirm that diagnosis. The patient's partial TBG deficiency was discovered

TABLE 1.—*Endocrinologic Studies of Proband, Aged 14 Months*

Time (minutes)	*Glucose Tolerance Test (glucose mg/100 ml)*	*Insulin Tolerance Test (glucose mg/100 ml)*	*Serum Cortisol during ITT* (normal 5 to 20 mμg/100 ml)*	*Human Growth Hormone during ITT* (normal >7.0 mμg/100 ml)*
0	100	100	30.8	1.0
30	..	40	28.8	4.5
60	122	58	..	1.0
90	..	84	..	9.8
120	108	94	..	1.8
180	86	..	..	..

*ITT—insulin tolerance test.

TABLE 2.—*Thyroid Studies of Family*

Family Member	*Serum Thyroxine (μg/100 ml)*	*Triiodothyronine Uptake (percent)*	*Free Thyroxine§ (mμg/100 ml)*	TBG§ *(μg/100 ml)*	PTC* *Response*
Proband	1.4-2.1	18.4, 18.1	2.0, 1.4	8.5	Nontaster
Female Sib	2.7, 3.1	19.8	2.1	7.0	Nontaster
Male Sib	5.6	10.2	1.7	20.0	Nontaster
Mother	2.9†, 1.7‡	18.4	1.0	8.0	Nontaster
Father	5.7	10.2	1.8	15.0	Nontaster
Normal values	3.5-6.5	10.0-14.6	1.0-2.1	10-26	

*Phenylthiocarbamide. †"During pregnancy." ‡"Post partum." §Bio-Science Laboratories.

during the neonatal period, and the possibility was considered that this abnormality might be associated with familial hypothyroidism.[6,7]

Hypothyroidism must be treated in early infancy if damage to the growing brain is to be avoided. The minimum laboratory studies needed for the diagnosis are measurement of the serum thyroxine level and of the triiodothyronine uptake, and calculation of the free thyroidal index (serum triiodothyronine-binding capacity × serum thyroxine). The free thyroidal index is closely associated with the measurement of free thyroxine—an expensive procedure, not universally available. Treatment should be initiated without awaiting the results of laboratory studies, and can be discontinued if the presumptive diagnosis of hypothyroidism is not confirmed. In the present case it was begun as soon as the infant's low serum thyroxine level was reported.

The diagnosis of hypothyroidism was brought into question by the normal growth rate, the normal bone age and the failure of thyroid to reduce the macroglossia or to raise the serum thyroxine to normal, and by the presence of macrosomia. Cessation of therapy was not followed by symptoms or signs of hypothyroidism, and did not alter growth velocity. Subsequent measurements of free thyroxine demonstrated that the infant is euthyroid. These observations, together with the detection of ear-notching and the flame nevi of face and nape, led to the diagnosis of Beckwith's syndrome. Fortunately, evidences of hypoglycemia never appeared; if they had, the delay in diagnosis could have been detrimental.

Total or partial deficiency of TBG has been described with increasing frequency during the last decade. It appears to be a common abnormality; Marshall and coworkers[8] concluded that it may occur in 3 percent of normal males. Since it causes no clinical or other ill effects, TBG deficiency is often unrecognized. TBG is not required for normal fetal development; an umbilical cord value of zero has been reported in a normal, euthyroid male infant.[9]

In TBG deficiency, thyroid function and the serum level of free thyroxine are normal, but the half-life of thyroxine is reduced by 50 percent.[10] Laboratory studies characteristically show a low serum thyroxine level and a high triiodothyronine uptake, with the free thyroidal index in the normal range. The combination of low serum thyroxine with elevated serum triiodothyronine is seen in only three situations: TBG deficiency; the presence of certain drugs including diphenylhydantoin, salicylates, 2,4-dinitrophenol, some thyroid analogues, or methyltestosterone; and in disease states characterized by severe reduction of serum proteins, such as nephrosis.[11] Radioactive iodine uptake is usually normal in TBG deficiency, although some patients have had inexplicably low values.[6,12,13] Treatment with desiccated thyroid or sodium L-thyroxine increases the basal metabolic rate without altering the serum thyroxine level, making it possible to produce clinical hyperthyroidism in a patient with a low serum thyroxine level.

In most studies of TBG deficiency, a method of direct measurement has been used which involves chromatographic separation resulting from the

affinity of radioactive thyroxine for TBG. A low value recorded by that technique may reflect either a true TBG deficiency or an abnormality in the TBG molecule that affects its binding with radioactive thyroxine. Marshall and Pensky,[14] using an immunologic technique, recently demonstrated that the precipitation line formed in agar by the serum of TBG-deficient subjects was identical to that of normal controls, suggesting that the defect is in binding serum thyroxine rather than in the absence of TBG. The validity of these observations has been questioned by Levy, Marshall and Velayo,[15] who could not reproduce the findings of Marshall and Pensky.[14] In neither study was a distinction drawn between patients with partial absence and those with complete absence of TBG.

The term *TBG deficiency* is applied to two disparate conditions: (1) an abnormality transmitted by an x-linked gene, in which affected males have a TBG value of zero,[6,9,12,16,19] and heterozygote females have intermediate values; (2) an abnormality transmitted probably as an autosomal dominant, in which affected males and females have low, equal, and measurable[10,12,17-19] levels of TBG. The TBG deficiency observed in the family reported here represents the second of these two types of abnormality.

By serendipity, this becomes the first description of a patient with Beckwith's syndrome and TBG deficiency. Whether this coincidence represents a true association cannot be determined until more cases are observed.

Summary

A two-year-old boy has had since birth a previously unreported combination of Beckwith's syndrome with familial partial thyroid-binding globulin deficiency. The infant and his family are euthyroid. Features suggesting hypothyroidism were macroglossia, and an omphalic abnormality. Differentiation of Beckwith's syndrome from hypothyroidism is important: hypothyroidism requires early treatment to avert brain damage; and the lethargy seen in some patients with Beckwith's syndrome is hypoglycemic.

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Community Medicine in California

A Symposium

EDITOR'S NOTE Community medicine *is a relatively new term in the jargon of medicine and health care. It is being used with increasing frequency in connection with new approaches to improving the delivery of medical and health care services to those who for one reason or another may not have been receiving their share. Even though the subject matter has not yet been clearly defined, community medicine is beginning to be taught in medical schools and programs and demonstrations are being conducted in medical practice and in the delivery of health care services.*

The editors of California Medicine *believe that a brief assessment and status report on "Community Medicine in California" may be helpful at this time. At the very least it can serve as a point of departure for further discussion, and perhaps as a beginning upon which to build. The method used to develop the material was a brief survey of the rapidly growing literature on the subject (which was not very helpful) and an invitation to each of the medical schools and the schools of public health in California and a number of others to submit brief statements concerning what they believed community medicine to be and their experience with it (which was much more helpful).*

The material to be presented therefore is an "Assessment of the Concept of Community Medicine" by the editor, together with several of the statements contributed in response to the previously mentioned invitation and from which the "assessment" is largely derived, and four articles giving examples of programs in community medicine which happened to be available for publication at this time. These examples, however, by no means reflect the full spectrum of the activities in community medicine in California at this time, nor are they all that has been published on this subject in California Medicine. *The editors would call attention to the following reports which were previously published in this journal:*

The Rural Health Program of Southern Monterey County, by Len Hughes Andrus, MD, February 1968

Mission Neighborhood Health Center, San Francisco, by George K. Herzog, MD, September, 1968

The Hunters Point-Bayview Community Health Service—A Project of the John Hale Medical Society, the San Francisco Chapter of the National Medical Association, by Arthur H. Coleman, MD, March, 1969

The San Fernando Valley Health Consortium—A Mustering of Community Resources for Health Manpower, by George J. Holland, PhD, and Addie L. Klotz, MD, MPH, January, 1972

A New Community Health Care Center—The Our Lady of Guadalupe Facility in Daly City, by Patricia Wright, December, 1972

Refer to: Watts MSM: An assessment of the concept of community medicine, *In* Community Medicine in California—A Symposium. Calif Med 118:68-71, Apr 1973

An Assessment of the Concept of Community Medicine

MALCOLM S. M. WATTS, MD

ANY ATTEMPT TO CONCEPTUALIZE what is meant by community medicine is at best hazardous if not indeed presumptuous at a time when there is so little of consensus among those who are most active in this field. Yet conceptualization, however crude, can often help to clarify thought and provide a measure against which what is being done can be evaluated. The approach here is to borrow freely from what is known to be going on in California and from the expressed thoughts of others who undoubtedly know more about the subject, and with this information attempt an assessment of the concept of community medicine.

We shall begin by listing some definitions and opinions, then put forth one person's view of an emerging concept, briefly consider what might be the subject matter of community medicine, allude to what is going on in California, and finally comment briefly on what could be a bright future for a fascinating specialty.

Some Definitions and Opinions

The following are some representative "definitions" of community medicine abstracted from the brief papers submitted for this report:

¶ Community medicine is regarded as the field which encompasses all health service needs of the community.
—T. TIMOTHY CROCKER, MD

¶ A precise definition of the term "community medicine" is still a subject of disagreement among public health planners, community health program administrators and other professionals close to the field.
—DONALD BRAYTON, MD

¶ Community medicine is that academic discipline which deals with the health of human populations and disease as it manifests itself in defined population groups.
—JOSEPH STOKES, III, MD

¶ Community health is the scientific study of the health problems of the community and the application of this knowledge to the solution of these problems.
—M. ALFRED HAYNES, MD

¶ Community medicine may be defined as a movement in medicine aimed at adapting medicine more closely to community needs, and this has a different focus from that of preventive medicine (individual or mass prevention of disease) or public health (organized community effort to advance health).
—DAVIDA TAYLOR, MD, MPH, and LESTER BRESLOW, MD, MPH

¶ Community medicine involves planning, provision for the delivery of services, patient education, manpower training, categorical activities, virtually all major aspects of the health care delivery system. Community medicine, in the Regional Medical Program (RMP) view, also involves every type of community and socioeconomic group, linked by the common thread of strong community involvement, in partnership with the providers in the development of services, from the moment they are first proposed.
—PAUL D. WARD

¶ From the point of view of the general public, community medicine may well be defined as the availability of health care and medical care with minimal social, economic, cultural, and environmental barriers.
—HAROLD MAZUR, MD

¶ Community medicine involves planning, organizing, financing and administering an organized system of medical care to a defined population. The scope of activity should include preventive, curative, and rehabilitative medicine. It should include provision for the necessary facilities to provide this broad spectrum of clinical services. Finally, to be optimally effective a community medicine program should be integrated into a comprehensive public health activity which addresses all the factors (social, behavioral, environmental and economic) which influence and determine the health of the population and its burden of disease.
—WARREN WINKELSTEIN, JR., MD, MPH

¶ Community health is a product of the medical profession's long history of attention to proper diagnosis and treatment of disease, comprising a complex and interrelated series of interests and activities that has been described as "the medical system," including the ability to pay for these services.
—NEMAT O. BORHANI, MD, and JESS F. KRAUS, PhD

The above definitions by no means reflect all of the ideas and opinions concerning what community medicine is or should be. Even a cursory survey of this field shows that there are other concepts which are more or less widely held. Some of these may be briefly stated as follows:

- Many medical students and young physicians seem to think of community medicine quite simply in terms of primary care and family practice in deprived communities.
- Some medical schools (not necessarily in California) seem to regard community medicine

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as that part of the student's clinical training which he gains through experience in a practice community.

- Some other medical schools (again not necessarily in California) view community medicine as a service obligation of the medical school toward those who live in the surrounding community.
- Some health care planners see community medicine in terms of cultural deprivation and poverty and the increased incidence of disease and disability which are to be found in these settings.
- To others community medicine appears to be an all-embracing concept of community participation and community control which will somehow rationalize the whole health care system.
- A number of medical societies (in California at least) seem to look upon community medicine as a means by which groups or communities, which for one reason or another have not been in the mainstream of medicine and health care, can be brought into it.

An Emerging Concept—One Person's View

While the varying definitions and opinions just cited are evidence enough that the concept of community medicine has not yet jelled, there is nevertheless much to suggest that a viable concept may in fact be emerging. Editors being sometimes brave and often foolhardy, occasionally move in where others are loath to tread, with results which may or may not be worth very much. This may now be the case since this editor will herewith attempt to express a view of an emerging concept of community medicine in terms which will be familiar and, he hopes, somewhat understandable and acceptable to physicians and others in the medical community.

In retrospect it seems clear that the current interest in community medicine grew out of the national determination to make high quality health care equally available to all, and the recognition that there are in fact identifiable cultural, ethnic, economic or geographical groups or "communities" which for various reasons have not been receiving the health care services they need. As these reasons were examined and studied in different groups or communities the nature of the unmet needs and the various barriers which have prevented them from being met have gradually become more apparent. The "community medicine movement" seems fully determined to understand and meet these needs, and it follows that the subject matter of community medicine will consist of the knowledge, technology and practice skills which are bound to be needed.

As it has developed to date, community medicine seems to focus upon identifiable groups or communities with definable cultural, ethnic, financial, geographical or other characteristics. Community medicine is concerned with primary health care for members of the group or community but beyond this with the health status of the group or community as a whole, and with the appropriateness and acceptability of the health care services which are available to it. The community health movement also tends to accept the World Health Organization definition of health as "a state of complete mental, physical and social well-being and not merely the absence of disease"; and with this there comes a blurring of the traditional distinction between medical care and health care. It is also noteworthy that both the public and private sectors are usually involved to a greater or lesser extent. But perhaps most important of all, the community or group to be served, as the "consumer," is found always to be directly involved as a full participant in whatever is to be done, much as is a patient in traditional medical care. In this connection it is increasingly apparent throughout the entire health care field that the "consumer," be he patient or a community, must now be fully informed and fully participating in his own medical and health care.

It is this last observation which suggests that the approach of community medicine to the particular health problems of any given community is in many ways quite similar to the approach of a clinician to the particular health problems of a given patient. If community medicine can be thought about in these more familiar terms, then it is suggested that what is meant by this term begins to take shape somewhat as follows:

- Community medicine is concerned with the health and health care of identifiable groups or communities which (like patients in other forms of clinical medicine) have their individual problems and their own particular characteristics.
- The classic principles of diagnosis, treatment, prevention and rehabilitation can be applied to the "patient" in community medicine, both at the personal and at the community level, and the community as "consumer" (or as patient) should

be involved in planning, in decision-making and in carrying out the treatment program.

- The science and technology of community medicine will include, in addition to a knowledge of clinical medicine, the special knowledge and skills needed to diagnose and treat the health care ills of many kinds of identifiable communities in collaboration with the communities themselves. This is largely a new field and will be concerned with the many barriers to good health and good health care to be found in various communities and with adapting the health care delivery system and other resources in the communities and elsewhere to overcome them.
- The role of the physician in community medicine goes beyond his traditional clinical role in patient care, to involve him in the "clinical" diagnosis, treatment, prevention and rehabilitation of those factors in a particular community which interfere with or prevent good health or good health care in that community. For this he will need new skills as manager, problem solver, organizer, skilled technician, advocate and active participant in a team effort.

The Subject Matter of Community Medicine

If the view of community medicine just described can be accepted as a kind of working hypothesis, it becomes possible to begin to identify some of its special subject matter. Community medicine is seen to embrace clinical medicine but to differ from it since it focuses on more than the health and ill health of individuals. It also differs from public health, environmental medicine and what is sometimes called social medicine, all of which are more concerned with the health and well-being of the public and society as a whole. However, community medicine clearly overlaps with each of these and interacts with each of them as they affect health and ill health in a given community.

Within this framework or hypothesis the special subject matter of community medicine seems likely to include much if not most of the following:

- The disciplines, technology and expertise involved in understanding and influencing community organization and community behavior for better health and better health care appear to be essential—that is, the human skills involved in dealing with a human community as a "patient."
- The disciplines, technology and expertise necessary to develop the data base which will define the community, assess its complaints, quantitate its needs and resources, develop and implement an acceptable treatment program to achieve or restore community health and measure what is accomplished—that is, apply the principles of diagnosis and treatment not only to the health care problems of individuals in the community but to the community itself.
- The prevention of ill health for a community, or indeed its rehabilitation, fundamentally requires that the community be integrated into the cultural, educational, economic and geographic mainstream of American society as well as into the mainstreams of American medical and health care services, thus eliminating the need for specialized community medicine for that community. The disciplines, technology and expertise of community medicine will therefore overlap with a much broader social responsibility for health and well-being.

The disciplines, technology and skills involved in subject matter such as this have largely yet to be developed. They will obviously be rooted in demography, epidemiology, biostatistics, sociology, cultural anthropology, economics, political science, health care systems, information science, primary health care, and perhaps most important of all in the technology and skills necessary to influence human behavior for the betterment of personal and community health. The opportunities are enormous not only for improving community health but for helping to realize, through community medicine, the American dream for many communities not yet in the American mainstream.

What's Doing in California

Many facets of a concept such as has been suggested are already under development in California under the aegis of medical schools, schools of public health, medical societies, or others, and more often than not with the help and financial support of government. The disciplines and subject matter of community medicine are being probed, the kinds of personnel which will be needed and the kinds of training they should have are being studied, and a variety of field demonstrations are in progress throughout the state. The scope of what is going on can be gleaned from the invited statements published as part of this "Assessment and Status Report" and from the reports of specific projects published in this and previous

issues of CALIFORNIA MEDICINE. No attempt has been made to be complete but there is enough to indicate the dimensions of this new and rapidly developing branch of medicine and the considerable progress that is being made in California.

The Future of Community Medicine

Dwight L. Wilbur, formerly Editor of CALIFORNIA MEDICINE, has recently editorialized [POSTGRADUATE MEDICINE, page 227, November, 1972] as follows:

> The practicing physician not only must care for patients who come to him in his office or the hospital, but he and his associates in the healing profession must also go into the community, find where the needs for prevention and care exist, define what the needs are, and see that they are met. This is a new role for the physician, and it is generally not clearly understood by him or by the organized profession. Performance of this role clearly takes time, education, change in attitudes and perspectives, and strong support and assistance from countless professionals, technicians, consumers and others.

For many reasons it would seem certain that community medicine indeed has a future, although somewhere down the road it could become obsolete if and when there are no longer identifiable communities with special cultural, economic, educational or geographic barriers to good health and good health care. This can occur only when the mainstream of society and of health care is all-embracing and even worldwide. Until this happens, if and when it ever does, the challenges for community medicine will surely be varied and continuous.

It is to be hoped that the future interest and emphasis on community medicine will not lead to too much compartmentalization in the delivery of medical and health care services. This is not likely to occur if the goal is to identify and overcome the special barriers to good health and health care in a community and to integrate that community and its members fully into the mainstream of American life and American health care. Any lesser goal can only be self-defeating, since it will only perpetuate the isolation of the community and with it its special social and health care problems. It is not entirely clear that the importance of emphasizing the need to integrate community with special problems into the mainstream is as yet fully recognized by the community medicine movement. It is to be hoped that this will occur.

The future of community medicine therefore appears bright. There is reason to believe that for some time to come it will play an increasingly important role in fulfilling a basic premise which is not to be denied, that modern medical care should be available and acceptable to everyone and that everyone should know how to use it. An increasing number of physicians will practice community medicine and it will profoundly influence medical education. It has already begun to do so. It will also involve an increasing number of allied health professional personnel. It will add to the overall cost of medical care. And of even greater significance, as its disciplines, technology and expertise develop, these will undoubtedly be found to have worldwide application. The potential exists for community medicine to become an important instrument not only for the betterment of health and health care but for improving the quality of life, first in this nation and then throughout the world. Significantly, California appears to be in the lead both in the variety of its programs and in the interest which has been developing in this subject.

Refer to: Stokes J III: Community medicine at University of California, San Diego, *In* Community Medicine in California —A Symposium. Calif Med 118:71-74, Apr 1973

University of California, San Diego

JOSEPH STOKES III, MD

THE DEPARTMENT OF COMMUNITY MEDICINE at University of California, San Diego, now five years old, was originally organized a year before the arrival of the first medical students in our School of Medicine. Since its origins in 1967 the Department has not only had to deal with the complex (and frequently frustrating) problems associated with establishing *any* discipline in *any* new medical school, but also has been swept up by the wave of social concern which was the "community medicine movement" of the 1960's. Indeed, this force has been so strong that it has markedly altered our original plans and has placed severe strains on our limited resources.

Community medicine's image is blurred by the

Dr. Stokes is Professor and Chairman of the Department of Community Medicine.

fact that it has several different definitions. We define it as that academic discipline which deals with the health of human populations and disease as it manifests itself in defined population groups. Therefore, the discipline has a *systems* rather than the traditional *individual* focus of both general and specialty medicine. We share our "herd" focus with the classical discipline of public health and preventive medicine, and in many ways community medicine is evolving as the link now bridging the gap which has developed between public health and clinical medicine over the last 40 years. Community medicine deals as much with health as it does with disease, and focuses on prevention and rehabilitation rather than on diagnosis and treatment. It is, therefore, more active at both ends of the medical care spectrum than it is with the diagnosis and treatment of severe illness. We deal with patients who, if not healthy, have as yet to be dominated by their disease. We also seek to rehabilitate those who are disabled so that they can again function effectively. Community medicine is also becoming increasingly dependent on the social and behavioral sciences since we apply various concepts such as sociology, cultural anthropology and economics in much the same way that clinical medicine applies concepts of organ, cellular and molecular biology. We also are borrowing techniques and concepts from newer disciplines such as operations research to help us dissect out the complexities of the health care system.

However, confusion arises since community medicine has also come to mean the attempt of medical schools to better define their service responsibilities in relationship to the communities that they serve. Within this context, several medical schools[1] have established Offices of Community Health Affairs as staff functions of the dean's office. Although such developments are laudable, such a function is quite distinct from the purpose of the academic discipline defined above. For instance, if such a school decides to assume responsibility for the health care of certain underserved population groups within its service area, such a commitment *must* be shared by all those clinical departments of the school involved with the provision of such services. Although such a program may better serve the Department of Community Medicine than other departments as a teaching and research resource, departments such as medicine and pediatrics must also be involved if personal ambulatory medical care services are to be provided by internists and pediatricians.

One pitfall of our discipline is that it is so broad that a department such as ours runs the risk of superficiality if it attempts to develop excellence in every facet of our discipline. Consequently, we have deliberately limited our departmental functions to the three divisions of Epidemiology, Health Systems, and Primary Medical Care[2] (see Chart 1). Our classical academic function is one

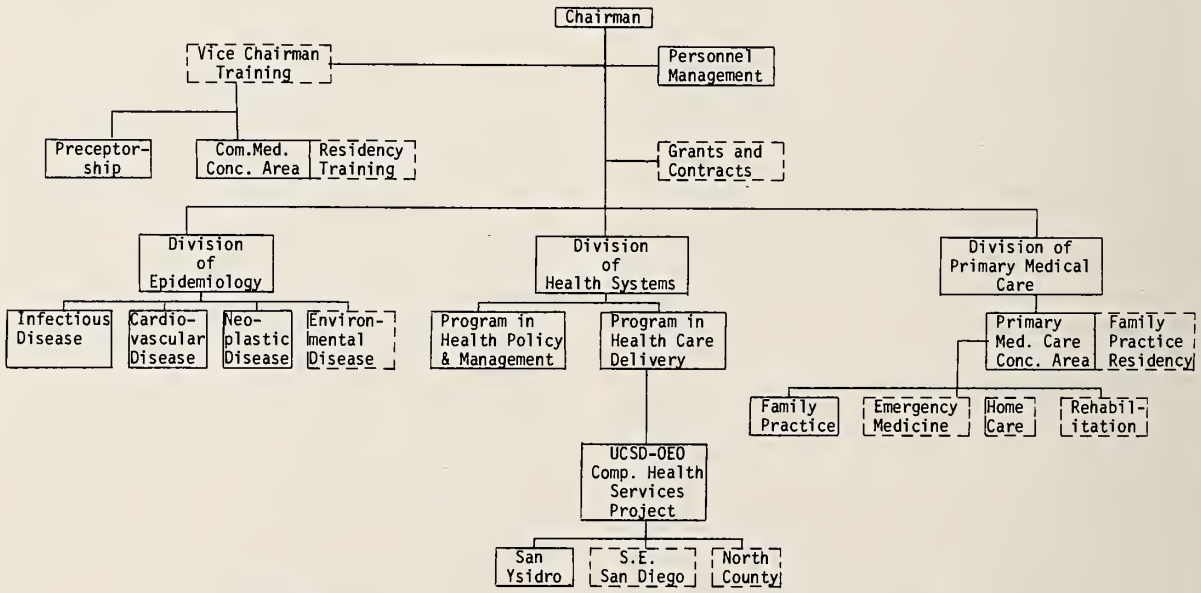


Chart 1.—Reorganization plan of department of community medicine

which encompasses epidemiology and biostatistics. This division not only teaches a course sequence to all second-year medical students which is closely integrated with concurrent sequences in pathology and microbiology, but it also provides consultation in experimental design and assists in epidemiologic surveillance of nosocomial infections at our teaching hospital. In conjunction with the Lipid Research Clinic of the Department of Medicine we are conducting a survey of the prevalence of hyperlipidemia in Rancho Bernardo, a planned community in North County San Diego. We are also helping to plan a long range dietary and drug intervention study to determine the primary preventability of atherosclerosis.

Our largest division is that of Health Systems, which is subdivided into a program in Health Care Delivery and a program in Health Policy and Management. The former program is that which developed our OEO Outreach Program which originally focused on the community of San Ysidro, a Mexican-American community adjacent to the international border, but which is also deeply involved in our Black community in Southeast San Diego and our underserved rural community in North San Diego County. Although UC,SD has served as the fiscal agent for this program during its first two years, by September 1973 we expect to shift to an advisory and consulting role and remove ourselves as a mere conduit of funds between OEO on one hand and the target communities on the other. Our role will remain that of liaison regarding professional staffing and we will continue to utilize these community health centers as teaching and research models for our programs of Family Practice and Health Services Research.

Our program in Health Policy and Management is currently developing a health status index and is planning a training program for selected undergraduate medical students and graduate students in health services administration. The entire division offers a course to all second-year medical students on the organization of health services which is required for all those who elect to concentrate their undergraduate medical education in our department.

Finally, our department also provides a focus for a developing program in Family Practice which is organized under our Division of Primary Medical Care. Rather than establishing a separate department of family practice as is currently being done at many medical schools, we have elected to develop a Division of Primary Medical Care which will coordinate a training program in Family Practice as a cooperative effort of the departments of Medicine, Pediatrics, Psychiatry, Obstetrics and Gynecology, and Surgery. This program will utilize not only hospital-based family practice clinics, but also community models as well. It is certainly clear to us that the usual out-patient department in a university hospital is a poor place in which to conduct both service and teaching programs in family practice. Thus we are developing a "field faculty" of practicing physicians who serve as preceptors for students during their field experience not only as fourth-year students concentrating in primary medical care, but also for medical students on summer preceptorships during the first two years. This preceptorship program is currently being elected by more than half of the students and is focused on the summer between their first and second year. Finally, we are also hopeful that this division will later be able to coordinate programs in Emergency Health Care as well as in Rehabilitation. However, at the moment our first priority is Family Practice.

Although we have centered our attention on the training of undergraduate medical students during the first five years, our current teaching plans involve the development of two graduate (residency) programs—one in Community Medicine and the other in Family Practice. The former residency will be designed for those who wish to pursue careers in academic medicine and also for those who wish to enter into sophisticated health services administration either in medical schools, in government service or the private sector. This residency will be of three years' duration with the first year focusing on Master's level training either in public health or in administration. The last two years will be concerned more with project work than field assignment including clinical experience for those who wish to elect such a rotation. The residency in family practice will aim not only to train family physicians in community practice but will also attempt to train those who wish to pursue careers as full-time faculty in one or another family practice training programs.

We have encountered a series of pitfalls during our first five years of experience, some of which are referred to above. First of all it has been difficult for us to communicate from time to time both with our faculty peers and with the medical stu-

dents not only because of our focus on the "herd" rather than on the individual, but also because of differing values and attitudes. We have also found that departments of community medicine are often expected to serve as advocates for social change. Although we believe that we do have a responsibility to create new models of medical care and to carefully analyze as to whether or not such models work better than those that exist, social medicine is not socialized medicine. Our goal is to provide data and a rational basis for community-wide decision-making and not to take strong advocate positions. In any case, to date we have been highly unsuccessful in effecting any substantial change in the intramural health care system at UC,SD. The chances are that we would be even less successful if we attempted such change in the San Diego community.

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University of California, Irvine

T. TIMOTHY CROCKER, MD

COMMUNITY MEDICINE is regarded by the California College of Medicine and, if I may be more inclusive, by the Irvine Campus of the University of California, as the field which encompasses all health service needs of the community. This concept is so broad that it includes services offered by persons who are not commonly educated by schools of medicine or even by university campuses. Accordingly, the Department of Community and Environmental Medicine has identified parts of the broad picture which seemed consistent with talents already present at UC,I. The process of identifying centers of interest and academic quality has been going on only since July 1, 1971, when the department was established. Activity in areas related to community medicine was found to be established in the College of Medicine in all departments. Examples are taken from the departments of Psychiatry, Pediatrics, Physical Medicine and Rehabilitation and Internal Medicine.

The Department of Psychiatry, with Dr. Louis Gottschalk as chairman, has strong connections with the Community Mental Health Services Agency of Orange County under the direction of Dr. Ernest Klatte. The Department of Pediatrics, whose chairman is Dr. Thomas Nelson, had active ties to the Orange County Department of Public Health and has developed programs for the school nurses of a number of the school districts of Orange County. The Department of Physical Medicine and Rehabilitation, Dr. Jerome Tobis, chairman, had joined forces with a coalition of community service agencies to establish better services to the disabled of Orange County.

The Department of Medicine, under the chairmanship of Dr. J. E. Berk, had signalled its interest in the process of primary care for patients entering Orange County Medical Center by recruiting Dr. Elsie Giorgi as Director of Ambulatory Care Services of the Medical Center and as a member of the Department of Medicine. Dr. Giorgi became an important member of the Department of Community and Environmental Medicine as well, and was in charge of the teaching program in community medicine for first-year students. Her move to UC,LA is regarded as a gain by that campus, but only a partial loss to UC,I, since she continues to be a member of the UC,I department.

The Departments of Obstetrics, Medicine, Pediatrics, Psychiatry and Surgery had joined then Dean Warren Bostick as an advisory group on behalf of the Family Practice Program, directed by Dr. Blair Pace; this program was incorporated by the Department of Community and Environmental Medicine. The process of training physicians for primary care cannot be done by a single department in a medical school, but the Department of Community and Environmental Medicine will share in this process by evaluation of local needs and student interest, and by assisting in setting up preceptorship opportunities for advanced students and Family Practice residency programs in affiliated hospitals.

Dr. Crocker is Chairman of the Department of Community and Environmental Medicine.

The College of Medicine is currently engaged in discussion and joint planning with the County of Orange to determine the scope and organization of the desired role of the University in the publicly organized health care system of this region. The College of Medicine earnestly seeks a role of leadership in such planning and is recruiting faculty with special interests in the planning of health care services. The curriculum of the medical student and the nature of post-graduate training will increasingly emphasize organized ambulatory care services to provide the educational experience necessary for practitioners in the 70's.

The Department of Community and Environmental Medicine set a tone for future development by incorporating into its area of teaching reponsibility the field of environmental toxicology. The Department's first appointee was Dr. Dwight Culver as Director of the Division of Occupational and Industrial Medicine. Dr. Harold Hodge was appointed, jointly with UC,SF, as Professor of Pharmacology and Toxicology with the cooperation of Drs. Elliott and Featherstone of UC,I and UC,SF, respectively.

Recently, the department was awarded a contract to manage and conduct research in the Toxic Hazards Research Unit of the Aerospace Medical Research Laboratory at Wright-Patterson Air Force Base. This contract carries with it a number of professional and technical personnel experienced in inhalation toxicology who have become part of the department and who will be engaged in collaborative work between that unit, the Department of Community and Environmental Medicine and investigators in several departments of UC,I, as well as at UC,SF, UC,D, and UC,LA. The capacity of the Department of Community and Environmental Medicine, of the Irvine campus and the University of California more generally, to develop basic and applied research and training programs in industrial and community problems of atmospheric pollution will be greatly enhanced by this affiliation. One aspect of Community Medicine, as served by the Department of Community and Environmental Medicine at UC,I, will become, therefore, a scientifically and technically oriented approach to physical, chemical and biologic health hazards in the environment. These should include within the Department of Community and Environmental Medicine and the College of Medicine, post-graduate training for physicians seeking board certification in Occupational Medicine, graduate and post-doctoral training in toxicology with emphasis on industrial and community exposure to toxic, carcinogenic and mutagenic hazards, and preparation of nurses, paramedical and technical personnel for this field.

The teaching activities of UC,I schools and programs outside the College of Medicine were recognized as important to the concept of community medicine. The department has participated by joint teaching and planning. The department has provided lecturers in health aspects of air pollution for the School of Engineering, has offered instruction in public health bacteriology for trainees under the Social Ecology Program, and seminars in medical care in community and industrial settings for students of the Graduate School of Administration. Coordination between the Department of Community and Environmental Medicine and other campus units will serve progressively to develop joint teaching activities at UC,I in several major areas of community medicine.

Refer to: Brayton D: California Regional Medical Programs—Area IV, *In* Community Medicine in California—A Symposium. Calif Med 118:75-77, Apr 1973

California Regional Medical Programs—Area IV

DONALD BRAYTON, MD

MANY PHYSICIANS who are privileged to interview applicants for medical schools have become aware during the past few years that an increasing number of these young people list "community medicine" as their ultimate goal. When asked to define this term, they describe one or another version of what most physicians would call family practice. I suspect few medical practitioners can define community medicine more accurately. Most, if they think of it at all, consider it a vague public health term associated somehow with barrios, ghettoes and out-of-the-way rural places. Despite

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its growing usage, a precise definition of the term *community medicine* is still a subject of disagreement even among public health planners, community health program administrators and other professionals close to the field.

Within the academic world the term is used broadly and has a variety of connotations. Many medical schools have established Departments of Community Medicine to give medical students field experience at a distance from the university medical center. Such experience may be obtained in neighborhood clinics or in other settings which may or may not be a part of a truly community-oriented medical project. Furthermore, the student may or may not be exposed to community medical organizational problems; usually he simply practices clinical medicine in the community setting to which he has been assigned.

Courses in community medicine in schools of public health constitute a vehicle for the student to reconcile and coordinate community health care needs with the available resources. Under this rubric the student also studies the regionalization of health services. This implies consideration of ways to equalize the quality and quantity of medical services among the various communities by (1) increasing the manpower and service capabilities of the communities themselves and (2) facilitating the two-way flow of medical expertise from centers of excellence to the communities and of patient referrals in the reverse direction.

If *community medicine* were used generally in the limited sense now to be described and illustrated, there predictably would be less confusion than now exists concerning the term. Assuming the word *community* is used either in its geographical sense or to denote a group of people having common social, ethnic or economic ties, *community medicine* then can be defined in either of two ways*:

1. The planning, provision and evaluation of medical care services to a community, or,
2. The delivery of health services in a community with concern about the population at risk.

In either case, the physician concerned with community medicine should be able to describe the population for which he is responsible, precisely, in the demographic sense. He should also have accurate knowledge concerning the nature and extent of the medical services the population is receiving and the nature and extent to which its health care needs are not being fulfilled. Although not all "health care needs" can be met by "medical services," it is important that the extent of both be consistently kept in view.

The physician who would undertake the discipline of community medicine must possess organizational capability and also must have (or have ready access to) demographic, epidemiological and evaluation skills. Obviously he also must have a source of funds. At present this source usually consists of reimbursement for medical services, or a government grant or a combination of the two.

If what is commonly practiced today is termed "individual medicine," it is apparent that the services delivered through community medical arrangements are individual medical services. Community medicine and individual medicine thus are interlocked and mutually supportive. The specialist in community medicine is essentially a medical organizer, administrator, manager or executive. However, by putting on another professional hat—if his time permits—he may also assume the more familiar clinical role of the physician by delivering personally some individual medical services within the community for which he is responsible.

The experience of Area IV of California Regional Medical Programs* has been interesting in relation to community medicine defined in this limited way. Most RMP operations have the potential for broad demographic impacts and are not targeted specifically toward the limited populations necessary to fulfill the above definition of "community." Consequently, all RMP health manpower programs, such as the training of pediatric nurse practitioners, and RMP projects calculated to improve generally the quality of health care, such as efforts targeted toward improving emergency medical services, must be considered too broadly directed to meet this definition of community medicine. Furthermore, even though each RMP program directed toward the improvement of the care of patients with categorical diseases has a definite target population (that is, all individuals having the disease) it does not seem reasonable to define this group of patients as a "community."

*Lewis, Charles E., MD, Professor of Medicine and Public Health, School of Medicine, University of California, Los Angeles; Director of Ambulatory Services, University of California, Los Angeles, Hospital. *Personal Communication.*

*Includes the counties of Madera, Fresno, Kings, Tulare, Kern, San Luis Obispo, Santa Barbara, Ventura and the southwest portion of Los Angeles County. Administered by UC,LA School of Medicine.

Dialysis, renal transplantation, stroke rehabilitation, mobile coronary care units and various screening activities are examples of this group of RMP projects. If these broad classes of programs, comprising a major part of the total RMP effort, are considered not to fall under the rubric of community medicine, are there any RMP projects that can be so classified?

In California RMP Area IV there are at least three programs which I believe can be properly termed community medicine endeavors according to the relatively narrow definition previously outlined. They are the Northeast San Fernando Valley Project, the Firebaugh-Mendota Project and the Ventura County Health Services Delivery Network. A brief description of each follows.

The Northeast Valley Project paved the way for a community health network for 250,000 residents of Pacoima, Sunland, Tujunga, San Fernando, Sylmar, Sun Valley and Lake View Terrace in the San Ferando Valley. This area is often referred to as a "health ghetto." Precise demographic measurements were made, data on the area's health needs were obtained and local services and facilities assessed. Priorities were established for development of the network, and community support by health professionals and consumers was generated. Following RMP development, this community health network has been placed in operation by the federal Office of Economic Opportunity.

The Firebaugh-Mendota Planning and Service Development Project is developing health care planning and delivery capabilities for the 15,000 residents of two adjacent farming communities in the Central San Joaquin Valley plus the migrant farm labor population. The Fresno County Medical Society, which has already contributed $10,000 to the project, acts as fiscal agent and provides overall direction, in cooperation with a broadly based community committee. Primary services will be provided in a health center staffed by volunteer physicians from the medical society and by residents from the Fresno teaching hospitals.

The Ventura County Health Services Delivery Network will serve 46,500 economically deprived residents of the county for whom health care is relatively inaccessible in their own neighborhoods. At present many of them must travel long distances to the County Hospital in the city of Ventura. The goal of the project is to improve the accessibility to health care for this group. A community health service center is being established in Santa Paula which will include decentralized eligibility billing and reimbursement for Medi-Cal patients. Other project components, to be phased in during the next three years, include the training of community workers to be employed by county agencies; training and employing at least 15 health counselors; establishing information and referral services; and augmenting the medical manpower capability of local hospitals by establishing a rotation program for family practice residents.

There is a definite and growing need for a precise definition of "community medicine" broadly acceptable to the practitioners, educators and students of the medical and public health professions. Otherwise this term—like so many others—will become a meaningless catch-all, eluding the standard of excellence so essential to its practical, purposeful and successful application.

Refer to: Mazur H: Community medicine at University of Southern California, *In* Community Medicine in California—A Symposium. Calif Med 118:77-79, Apr 1973

University of Southern California

HAROLD MAZUR, MD

A DEFINITION of community medicine will depend greatly upon the person or group asked to provide the definition. From the point of view of the general public community medicine may well be defined as the availability of health care and medical care with minimal social, cultural, economic, and environmental barriers. If one were to focus further upon that segment of the public considered to be economically and socially underprivileged, one would have to add an additional component to the above definition—that is, community involvement, participation (and, in the opinion of some) control of the implementation of such health and medical care.

At USC, the Department of Community Medicine and Public Health has the three traditional obligations shared by all other departments of

Dr. Mazur is Chairman of the Department of Community Medicine and Public Health.

the School of Medicine, namely, education, service, and research. The historical development of this school of medicine, its long-standing relationship with and dependence upon the large and loyal clinical faculty, and finally its equally long-standing integrated affiliation with the Los Angeles County hospital system has made it possible to implement the school's service obligations on a medical-schoolwide basis, rather than through one of its departments. Thus, the obligations of this Department of Community Medicine are focused upon education on the undergraduate level (medical student) and the graduate level (intern and resident). Postgraduate education at this medical school has received particularly successful leadership from a special program of departmental status. Since community service is a fundamental obligation of all departments of this school of medicine, it was felt that the research efforts of this department should be directed to various programs involving the development and evaluation of model health care programs.

The purpose of the Department of Community Medicine and Public Health, University of Southern California, is as follows:

1. To help prepare the student physician to integrate social, economic, cultural, and environmental factors with states of health and disease within defined communities or population groups in relation to the daily practice of medicine.

2. To provide such services to the community which are consonant with the educational and research obligations of the Department.

3. To perform epidemiologic research basic to the above relationships and to the delivery of comprehensive health care.

The above represents the traditional role of this university in the fields of education, community service and research. A summarized survey of each of these follows.

Education

The Department of Community Medicine has been allocated time in the curriculum during the first of the four undergraduate medical school years, as well as a place in the third and fourth year continuum. Time constraints in the crowded curriculum of Year I made it necessary to employ a didactic approach and bring representative segments of the community to the classroom.

To implement the purposes listed above, four major fields have been delineated for undergraduate medical study.

1. *States of Health and Disease*—the causal factors, extent and distribution of individual, family, and community health problems and relate these to:

2. *Medical-Social Issues* such as employment, income-level, education, family stability, culture, human behavior, and legal and political constraints.

3. *Medical Ecology*—the fact that disease in the individual is also part of disease in the community, requiring application of the principles of disease prevention and control as they relate to individuals, populations, and the environment.

4. *Provision of Health Care*—starting with the doctor-patient role in clinical medicine and when and how this extends into the family and community, includes the principles of community organization for health promotion, maintenance, and protection. The role of government, voluntary and professional organizations on planning comprehensive health care, including manpower, facilities and delivery systems.

At present these curriculum objectives are introduced as a series of weekly two-hour lecture, panel and small group sessions during the whole of the first undergraduate year.

These discussions have utilized a selected list of topics in order to highlight the four major fields listed above. The selected list of topics covered in Year One is as follows:

1. Race, Ethnicity, and Health
2. Society, Sex, and Health
3. Society and Sickness
4. Poverty, Privilege and Health Care
5. Politics of Health Care
6. Legislation and Health Care
7. Solo Practice of Medicine
8. Group Practice of Medicine
9. Hospital Systems—Governmental, Voluntary, Proprietary
10. Public Health Agencies—Voluntary, Official
11. Medical Economics
12. Medico-Legal Issues in Health Care
13. Health Manpower
14. Trends in Health Care Delivery
15. Comprehensive Health Planning
16. Regional Medical Programs
17. National Health Insurance Proposals
18. Existing Health Insurance Carriers—Blue Cross, Blue Shield, Commercial Companies
19. Social Welfare and Public Health
20. Medical Records
21. Health Care in Europe and Other Foreign Countries

It is also the obligation of this department to introduce to the student basic biostatistical and

and epidemiologic methods in the study of health and disease. This is accomplished in the traditional lecture-laboratory method.

During the third and fourth year continuum, the students will have opportunity to elect one of several clinical clerkship options of six weeks duration sponsored by this department. Such clerkships will include individualized preceptorship assignments in the following:

- Hospital ambulatory care programs
- Solo, private practice offices
- Group practice offices
- Prepaid health care systems
- Community health centers
- Other specially arranged programs

The objectives of these clerkships are to (a) implement the stated goals of the department; (b) expose medical students to other health professional personnel, and (c) demonstrate the importance of patient care teams.

Community Service and Research

Since, as stated earlier, service is an obligation of the entire School of Medicine, it was felt that this department should emphasize exploring newer and contemporary methods of providing health care in the neighboring communities. This would not only widen educational opportunities for our students, but if successful would contribute to improved health care on a preventive and therapeutic basis to a variety of socio-economic levels of our local population.

The following is an abbreviated list of programs and activities developed under the leadership of individual members of this department during the past four to five years.

- Establishment of neighborhood health centers—for example, the South Central Multipurpose Health Services Center (OEO funded).
- Development of "Med Ocho," that is, a "hospital within a hospital" wherein the program of an entire hospital floor at the Los Angeles County/University of Southern California Medical Center is oriented to the East Los Angeles community.
- Training grants supported by the Commonwealth Fund and by HEW and designed to demonstrate: (a) the significance of allied health personnel in patient care teams and (b) an experimental approach to team teaching and team learning involving both medical and allied health students.
- A program designed to inventory the existence and availability of health care resources of both public and private nature in Los Angeles County with the aim of providing a computerized information and referral system.
- Various summer work projects for students intended to provide supervised field experience in community health problems.
- Finally, there are a number of programs in various stages of planning by members of this department who have primary or joint appointments in other departments of this medical school or in other schools of this university. These plans are oriented mostly in the study of health care needs, or in providing pilot programs designed to help meet such needs.

Refer to: Haynes MA: Community medicine at Drew Postgraduate Medical School, *In* Community Medicine in California—A Symposium. Calif Med 118:79-81, Apr 1973

Drew Postgraduate Medical School

M. ALFRED HAYNES, MD

COMMUNITY MEDICINE is the scientific study of the health problems of the community and the application of this knowledge to the solution of those problems. It uses such sciences as epidemiology and statistics in the definition of problems. In addressing the medical and health care problems of the community it applies, for example, the principles of preventive medicine and health care administration.

The unit of study and practice is usually a more or less well defined geopolitical entity rather than an individual. In this respect it differs on the one hand from clinical medicine which focuses on the individual, and, on the other hand, from social medicine which focuses on society in general. Because of its concern with health and disease in groups of people, one of its important considera-

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tions is that of the organization and provision of medical care to the community. It is not restricted to prevention, and therefore should not be confused with preventive medicine. It is concerned with the entire range of health care, but as it relates to groups rather than to individuals. A single case of appendicitis is not an appropriate concern for community medicine, but a single case of diphtheria might well be. On the other hand, if there were a higher frequency of deaths from appendicitis in a given community than would be expected under normal circumstances, this would be a matter of concern within the field of community medicine. In either of these circumstances—the case of diphtheria or the higher frequency of deaths from appendicitis—experts in the field of community medicine could be called upon to diagnose the problem and prescribe the appropriate treatment. In the case of the problem of higher frequency of deaths from appendicitis, the problem may not be entirely a matter of medical science. Instead, there may be problems related to the availability of medical care, the kind of services which are provided at institutions and the proper use of health manpower.

The domain of community medicine includes both the persons and the environment of the community. For this reason it is often confused with public health. In one sense community medicine can be considered to be identical with public health if one defines public health as the health of the public, but traditionally one thinks of public health as operating with the public sector of medicine (the official health agencies), in clear demarcation from the private sector. Community medicine bridges this gap and seeks to involve both the public and the private sectors of medicine in an integrated approach to the health problems of the community.

The term *community medicine* is so simple and so appealing that any patient who lives in a community or any physician who practices there is tempted to consider himself an instant expert. Such liberties are not taken with being considered a pediatric cardiologist, or an epidemiologist, but in fact, community medicine is a special branch of medicine and requires special knowledge and skills and therefore special training. One reason community medicine is not always considered a specialty is partly in the way it is practiced. Community medicine, as it is practiced today, seeks to involve the consumer as a full participant. Professionals in the field recognize not only their own expertise, but also recognize the expertise which consumers may contribute by virtue of being consumers.

Community Medicine at Drew Postgraduate Medical School

The Department of Community Medicine at the Drew Postgraduate Medical School is the only known department of its kind which was conceptualized as a result of interactions between a group of national experts and members of the community to be served. The initial grant for designing the department was provided by the Markle Foundation. The Regional Medical Programs, in one of its unique and innovative departures from the categorical approach, has supported many of the activities of the department.

As a means of addressing itself to the health problems of this community, the department has been concerned with the development of a system of health care in the area served by the Martin Luther King, Jr. Hospital and the Drew Postgraduate Medical School. The King Hospital, a community hospital within the Los Angeles County Hospital system is a new and important center of care within the area. There are other smaller and older centers of primary and secondary care within the area, such as the Watts Health Center. The Department of Community Medicine seeks to facilitate the coordination of existing resources for care within the area with the aim of providing those services which can best meet the needs of the community and diminish or eliminate existing problems. To do this, the department conducts a continuous analysis of the health problems of the community. These problems may be either disease problems or problems in obtaining care, such as problems of access. The department conducts a continuous analysis of resources especially in the area of manpower resources and facilities. This analysis leads to action. For example, recognizing the shortage of physician manpower in the area, the department developed the first program in California to train assistants to the primary care physician. In this way it hopes to contribute to both the quantity and quality of services provided to the community.

The quality of services provided to the community depends upon continued competence of the providers of care, and through its division of

Continuing Education the department provides opportunities for health practitioners of the area to enhance their knowledge and skills.

It is felt that better organization of providers can result in better care for the consumer. For this reason the department also provides assistance to groups of physicians seeking to organize themselves for more efficient service.

The department is especially interested in the evaluation of ambulatory care. One division participates in the evaluation of neighborhood health centers for the Office of Economic Opportunity. The department also participates, upon request, in the evaluation of ambulatory services within the hospital service area.

The department is also concerned with health services research and is conducting a study to determine which of the tasks now performed by physicians could be appropriately delegated to other categories of health personnel. This kind of research is also intended to influence the education of various types of health workers and the career opportunities especially in the field of allied health.

The health problems of our community cannot be solved by a narrow focus on health. Recognizing this, we have chosen as our primary goal working with the community to improve both health and welfare. Consistent with this goal we have at times taken unorthodox approaches for a department of community medicine. An example of this is our involvement in the development of a community buyers' club for the economical purchase of food.

Many of the service or research activities of the department can provide learning experiences for physicians interested in becoming specialists in community medicine and the department expects to start its residency program next July.

Financially, the department is supported by funds from several sources, including Los Angeles County, and special programs of the Federal Government including the Regional Medical Programs, the Bureau of Health Manpower, the Office of Economic Opportunity and others. The greatest support, however, comes from the local community, for the department defines community medicine as the department and the community working together to solve the health problems of this community.

Refer to: Winkelstein W Jr: A view of community medicine from UC School of Public Health, Berkeley, *In* Community Medicine in California—A Symposium. Calif Med 118: 81-82, Apr 1973

A View of Community Medicine from UC School of Public Health, Berkeley

WARREN WINKELSTEIN, JR., MD, MPH

DURING THE LAST FEW YEARS, the health and disease care fields have been increasingly burdened with semantic confusion. I would like to support this statement with three examples. First, antonyms have been converted to synonyms, the most glaring example being the use of the word "health" as a synonym for "disease," as in the phrase "health care." Second, acronyms have proliferated to the point that the identity of the source is obscured or forgotten. For example *HSMHA* (pronounced, his-ma-ha) for Health Services and Mental Health Administration—an agency which, incidentally, is more concerned with disease than health. Third, traditional institutions or activities have been renamed to make them appear new or, perhaps, to improve their public image. This has been done in the case of "family practice," a new name for an old activity, namely, general practice. Too little attention has been given to the consequences of such linguistic aberrations.[1,2]

In my opinion, community medicine is another example of renaming an established activity in order to improve an image and, perhaps, overcome biases in organized medicine that might obstruct its development. Community medicine is the organization and delivery of medical care to the population, which has been a recognized concern and part of the field of public health for a long time. Community medicine should not be confused with the terms *community health* and *public health* which are the more global terms appropriate to describe the entire spectrum of health and disease effects and concerns.

While the roots of concern and involvement of the public health movement in the organization and delivery of medical care to the population can be traced back to the nineteenth century, the cur-

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rent activity is a direct outcome of the monumental work of the Committee on the Costs of Medical Care. This group, working over a period of six years, from 1927 to 1933, produced 28 volumes which contain the justification and prescription for such activities as group practice, health maintenance organizations, quality control of medical practice, regulation of hospitals and nursing homes, provision of preventive medical services, improved medical, nursing, and auxiliary training, group payment, and indeed a total national health (medical care) service.[3] It is not surprising that the committee, its reports, and many of the proposals arising from them, were anathema to much of organized medicine. Fortunately, time has allowed a more objective view to be taken of these matters and, while some of the issues remain volatile, there is general agreement that the organization and delivery of medical care on a community or social base are legitimate concerns of the medical as well as the public health establishment.

Earlier I asserted that a distinction should be made between community or public health on the one hand and community medicine on the other. This position is based on a model of the relationship between health and disease and their care-systems which is illustrated in Chart 1. Health and disease are viewed as a continuum with "optimum" health at one end and death at the other. The intermediate points on the spectrum are altered health states, preclinical, and clinical disease. There are a variety of inputs into this system which influence each individual's position in it. It seems obvious that only some of these inputs are medical. In fact, a strong case can be made that the most influential inputs are not medical but rather genetic, environmental, social, behavioral and economic.[2,3] Some of these inputs are planned and purposefully applied and some are completely uncontrolled by the individual. In my view the total pattern of interaction—purposeful, and uncontrolled, medical and non-medical—should be the perspective of community or public health, while only those activities which are purposeful and clinical should be considered medical care and their organization and delivery be called community medicine.

Thus, community medicine involves planning, organizing, financing, and administering an organized system of medical care to a defined population. The scope of activity should include preventive, curative, and rehabilitative medicine. It should include provisions for quality control and evaluation of coverage. It should also include provision for the necessary facilties to provide this broad spectrum of clinical services. Finally, to be optimally effective a community medicine program should be integrated into a comprehensive public health activity which addresses all of the factors—social, behavioral, cultural, environmental, and economic—which influence and determine the health of the population and its burden of disease.

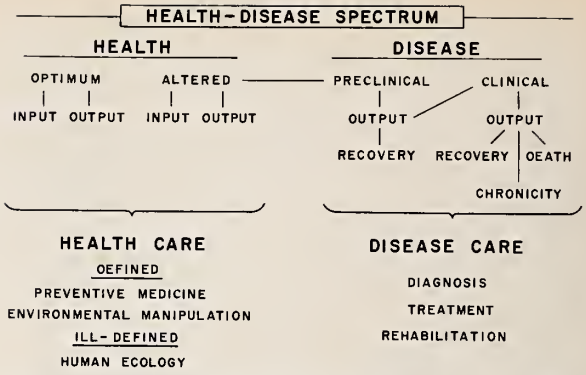


Chart 1.—A model illustrating the relationship of health and disease and their care systems.

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Refer to: Taylor D, Breslow L: Community medicine at University of California, Los Angeles, *In* Community Medicine —A Symposium. Calif Med 118:82-85, Apr 1973

University of California, Los Angeles

DAVIDA TAYLOR, MD, MPH *and* LESTER BRESLOW, MD, MPH

COMMUNITY MEDICINE has recently become one of the most rapidly growing aspects of medical education in the United States, suddenly appealing to a large number of medical students and faculty.

It may be defined as a movement in medicine

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aimed at adapting medicine more closely to community needs, and thus has a different focus from that of preventive medicine (individual or mass prevention of disease) or public health (organized community effort to advance health). This new movement in medicine is responding to such complaints as: decline of the family physician, with relative overemphasis on other specialties; inadequate physicians in "underserved" areas, with abundance in Beverly Hills; academic medicine an "ivory tower," pursuing its own agenda not related to the health needs of people; too few Black and Spanish-speaking physicians and other health care personnel to adjust medicine to large and growing minority groups in the population.

The effort to overcome the problems represented by these complaints takes many forms, including academic changes. At UC,LA the strategy involves the entire Center for the Health Sciences.

All the health professional schools at UC,LA have embarked on serious programs to recruit minority students: 36 among 179 entering graduate students in public health in 1972 were from minority groups, 23 of 144 entering students in medicine, 23 of 105 in dentistry, and 22 of 166 graduate students and 30 of 102 undergraduate students in nursing.

Approved family practice residency training programs have been established through the initiative of UC,LA Department of Medicine faculty members at three hospitals associated with UC,LA. A recent "Evening With Family Medicine" organized by the director of the Santa Monica Hospital Family Practice Residency Training Program, a member of the faculty of the Department of Preventive and Social Medicine, attracted more than 150 medical students.

Community Health Services

The School of Dentistry has for several years staffed with faculty and students a dental clinic in Venice, organized and directed by the Venice Health Council following a community health survey conducted by UC,LA public health and other students which disclosed that dental care was a high priority community need. More recently the UC,LA School of Dentistry has undertaken, jointly with the USC School of Dentistry, to operate a week-end mobile dental service for people in need in rural parts of southern California. A dentist who is now a candidate for the Doctor of Public Health degree in the School of Public Health has a major responsibility in this mobile program.

Many UC,LA students and members of the faculty volunteer considerable amounts of time in the many "free-clinics" in Los Angeles. Recent graduates and current faculty and students are now engaged in planning for a broad-based community health service in the Venice area. These activities tend to draw together students and faculty from the various health professional schools toward understanding and contributing to the solution of community health problems.

Curriculum

While the above-mentioned activities reveal the growing commitment of UC,LA as a whole to community medicine, the Department of Preventive and Social Medicine in the School of Medicine and the School of Public Health are particularly concerned with curriculum in this field. For some years these two academic elements have operated as a consortium faculty, for example, in teaching epidemiology to students in the School of Medicine and in the School of Public Health. They now have responsibility for a new course in Social Medicine for first-year medical students which will provide attention to (1) problems of minority segments of the population in obtaining medical care; (2) economic and social barriers to health care and current proposals for overcoming them; (3) primary care and new ways of providing it; and (4) special problems of migrant workers and others.

Following the course in Social Medicine during the Spring Quarter of the first year, students have an opportunity to obtain ten-week summer apprenticeships, mainly assisting in health care at places remote from the medical center. During the 1972 Summer, 20 UC,LA medical students worked in such situations as the rural Alaska health service, Indian reservations, farm workers health clinics, a community hospital having special language and other cultural problems with patients, and a small community in Oregon (to continue work in a "free-clinic" initiated by previous UC,LA students and supported by local physicians and the health department). Each student is supervised by a local physician and maintains contact with a faculty member during the summer. These experiences give students knowledge of some social aspects of medicine, experience in working effectively with people, and an

exhilaration for tackling major problems in medicine. More than 50 medical students in 1972 competed for the 20 places available in the apprenticeship program.

UC,LA also encourages medical students to participate in health work in other countries through a program sponsored by the Association of American Medical Colleges. For 1973, two students from UC,LA have been selected among 20 in the nation to work for ten weeks in the Yugoslavia health care system.

In the third-year pediatric rotation all students visit Venice and Imperial County for direct exposure to problems that people in poverty communities encounter in obtaining health care and various attempts to deal with these problems.

During their fourth year UC,LA students again have substantial opportunity to engage in social medicine, through preceptorships with (1) family physicians practicing in a rural or urban poverty neighborhood, a program initiated by a grant from the California Medical Education and Research Fund of the California Medical Association; (2) a family practice residency training program in a hospital located near UC,LA; (3) a college student health service, especially for study of health problems among adolescents; and (4) faculty members on special projects—for example, an excellent study by two students (one interested in psychiatry and one in public health) of emergency care services for the mentally ill patients in West Los Angeles.

Residency Training

UC,LA also offers an AMA Specialty Board-approved residency training program in preventive medicine, consisting of one year in clinical training, usually in some aspect of primary care provided by a UC,LA-related facility; one year devoted to work for the Master of Public Health degree in the School of Public Health; and one year to further study and experience involving a specific project in the field of preventive medicine. At present residents are engaged in: (1) development of a community health network, primary care linked with specialty and hospital care, under the auspices of an OEO-financed and consumer-led community health group; (2) a large-scale methadone treatment program for heroin addicts, extending from the campus into the community, under the auspices of the Department of Psychiatry; and (3) planning and initiation of a new family-oriented general medical service in a poor neighborhood, to replace the fragmented clinic services previously offered by Los Angeles County (as by most local health departments) in past years.

Research

Faculty at UC,LA have developed major investigations of such questions as the extent to which various types of health care plans (provider-sponsored, commercially-sponsored, and group practice-prepayment) meet the needs of their subscribers as viewed by those subscribers, as judged by provision of preventive medical services, and in other ways. Contracts with governmental agencies support efforts to determine the effectiveness, efficiency and other aspects of governmental medical care programs.

Graduate students, with faculty support, are engaged in such studies as: the extent to which new family practice residency training programs are achieving their objectives as seen by administrators, clinical teachers and residents; how those responsible for labor-management health care funds can evaluate the plans on which these funds are expended; how new types of health care personnel can be developed with emphasis on incorporating people living in the neighborhood being served into the health care system.

At UC,LA, therefore, the academic phase of community medicine—developing new types of service, education of physicians and other health care personnel in the ways of community medicine, and research on problems of community medicine—extends widely through the faculty and student body of the several schools in the Center for the Health Sciences.

Beyond that Center, the effort has increasing support among faculty of such schools as the Graduate School of Management and the School of Architecture and Urban Planning in helping to solve community medical problems. The National Health and Environmental Law Program (NHELP) on the campus has been deeply involved in securing the rights of persons eligible for public medical care programs, especially when these are impaired by administrative processes.

Off the campus, UC,LA is further related to community medicine—for example, through affiliation with the Department of Community Medicine at the Drew Postgraduate Medical School in

Watts. Members of the latter faculty have joint appointment at UC,LA and take part in the teaching program there; students and faculty from UC,LA take part in projects at the Drew School. Informal relationships extend from UC,LA to many other agencies engaged in community medicine including the Los Angeles County Department of Health Services and some of its hospitals and other units.

Thus UC,LA is participating on many fronts in the movement known as community medicine, to adapt medicine more closely to the needs of communities.

Refer to: Borhani NO, Kraus JF: Community medicine at University of California, Davis, *In* Community Medicine in California—A Symposium. Calif Med 118:85-87, Apr 1973

University of California, Davis

NEMAT O. BORHANI, MD *and*
JESS F. KRAUS, PhD

THE CONCEPT OF A Department of Community Health in a medical school must be viewed in terms of the total mission of a medical school. Departments of community health should provide opportunities for students to learn about, and participate in, the delivery of health care. These opportunities would provide medical students with an invaluable window to the realities of medical practice that await them as graduating physicians of tomorrow.

In offering a definition of the function and purpose of departments of community health, it is perhaps useful to distinguish community health from public health—both products of traditions that are compatible in principle, but quite divergent in focus. As has become apparent in recent years, the maintenance of health and protection from disease is considered as a guaranteed right of each individual rather than a privilege. The implementation of programs dealing with maintenance of health and prevention of disease has been vested to the government agencies; national, state, and local. The function of these agencies has evolved and increased over the years to cover an entire spectrum of varied activities dealing with environmental sanitation on one hand and prevention of disease (and sometimes treatment—for example, venereal diseases) on the other. Most recently these agencies have become quite concerned and interested in methods of payment and financial aspects of medical care as well. Community health, on the other hand, is a product of the medical profession's long history of attention to the proper diagnosis and treatment of disease, comprising a complex and interrelated series of interests and activities that has been described as "the medical care delivery system," including the ability to pay for these services. Recent advances in medical technology, however, have promoted changes in the social and demographic composition of the population such as age distribution, increase in urbanization and higher levels of income and educational achievements. These changes, in turn, have created a demand for a special kind of medical care delivery both in scope of delivery and in financing. Also, these changes, along with their dramatic publicity, have caused the emergence of an informed and highly vocal public, concerned with issues that affect its health.

We believe that the medical profession's long-established concern for the individual patient and its recognition of these changes have led to the recently identified set of priorities that in themselves have encouraged the establishment of new departments in schools of medicine, known as departments of community medicine or community health.

A definition of community health, therefore, offers a deliberate formulation of a proposal, broad enough to anticipate insights still to be achieved within the entire philosophy of medical education. This proposal denotes a matrix of concern embracing the ecological, social, and economic aspects of the community. Hence, we consider departments of community health those academic and administrative units in medical schools that can best represent the concept of health as a dynamic, non-static force in the communities. It

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should be emphasized that in the context of this definition, the departments of community health have at their foundation the concept of a unified and comprehensive health delivery system for the entire population in the community and not just the individual. These departments, in our opinion, represent that discipline within the medical school that provides, in total integration with other departments (preclinical and clinical), learning opportunities for medical students in a community setting.

The function of the departments of community health must, then, be interdisciplinary in nature. Since health itself is the result of constantly reacting forces, the occurrence of illness in individuals, and its distribution in the population, can be understood best by careful epidemiological considerations of multiple causes and factors constantly influencing man and his environment. To this extent, therefore, epidemiology is viewed as the scientific discipline basic to community health and is as essential in the medical school curriculum as all the other sciences basic to other branches of medicine.

Purpose, Goals and Objectives at UC,D School of Medicine

The purpose, goals, and objectives of the Department of Community Health at Davis are embodied in the principle that we must concentrate on the organization of health facilities and resources in order to effect economic and efficient community programs of comprehensive health care for all.

Naturally, the Department of Community Health at Davis is committed to a bias favoring preventive rather than strictly remedial medicine. And toward that end we have continued to cultivate a special sense of purpose in addressing our energies to problems amenable to community-wide solution, recognizing that our students should no longer be trained exclusively on the selective and biased sample of diseases they encounter within the confines of the University Medical Center. Rather, we believe, they should be given an opportunity to go out into the community and study problems of health and disease in the "patient's" own surroundings and habitat. From its inception, the UC,D Department of Community Health began its activities on the premise that neither the department of community health, nor the school of medicine can make its contributions in a vacuum, and that our dream can be nurtured and realized only with complete and unselfish integration of our energies with those of other departments in our school, utilizing fully all recent advances in scientific medicine. We in the Department of Community Health at Davis have committed ourselves to the concept that our society's future physicians must be qualified clinicians, counselors, scientists, and, above all, leaders in the community where they live.

Highlights of Activities of the Department

The activities of the Department of Community Health at the Davis Campus are in teaching, community service, and research.

Our plan for curriculum development, both realized and projected, includes the following elements: (1) an introduction to the concepts and philosophy of community health as early and as intensively as possible; (2) development of the student's clinical experience, relying heavily on a joint effort with other departments of the UC,D School of Medicine; and (3) establishment of effective community laboratories for student participation in both the core and elective curricula.

One of the important concepts introduced by the Department of Community Health in the structure of our school's core curriculum is that the basic principles of epidemiology be taught to medical students as soon in their educational experience as possible. The reason for this is our belief that medicine consists of three essential types of activities—*preclinical sciences* based in the laboratory, *clinical sciences* based in the hospital wards and clinics, and *preventive and social medicine* based in the community. None of these three activities is entirely independent, and our medical school curriculum approaches all three in an integrated and cohesive fashion. Just as physiology, biochemistry and anatomy are considered essential basic science material in the clinical teaching, so is epidemiology necessary for understanding preventive medicine. In addition, it is our belief that familiarity with basic principles in epidemiology provides medical students with the background needed for determination of the direction of medical research and the organization of effective health services in the community. Teaching basic principles in epidemiology does constitute, therefore, the major commitment of the Department of Community Health in the teach-

ing of core curriculum. Our teaching method of epidemiology is not isolated lectures or seminars; it is, rather, a problem-oriented, patient-based and community-centered presentation of issues relevant to the specific material which is being taught under the core curriculum. By using this method of teaching we have found that epidemiology becomes relevant to the total curriculum of the school and elicits active student interest and participation.

Other than core curriculum, the Department of Community Health provides students with the opportunity to select from among many and diverse elective courses. These include advanced courses in epidemiology, environmental health, health care delivery, financing, and, of course, participation in community health programs including the opportunity for participation in programs outside the geographic boundaries of the School of Medicine at Davis.

One of our most rewarding achievements in community service has been the development of a demonstration program to deliver comprehensive health services to seasonal agricultural workers and their families (the Yolo County Migrant Workers Health Program). The program was developed with one specific objective: to demonstrate the feasibility of setting up a model program and, once it became viable, to turn over its administration to the community. This objective was achieved and the program now has become a model for expansion into a multi-county Regional Rural Health Program, administered exclusively by local community leaders. Other examples of community service include participation in planning and organization of comprehensive health programs, regional medical programs, and free clinics.

It is important to note that the degree of involvement of a department of community health in different community service programs depends upon the available resources and manpower and is usually dictated by the pressing issues of the time and place. Therefore, one cannot describe these activities in specific terms. No two communities are alike in their needs for community health programs. Departments of community health should be receptive and responsive to the needs of their communities and consider their active participation in the community services. It has been our experience that involvement in such activities serves not only as an effective instrument in discharging our responsibilities to the community, but also provides us with an excellent vehicle for teaching. Students gain inestimable satisfaction from participation in such community programs.

The setting for research activities of the Department of Community Health must be the community itself. The research activities and programs have been directed into two general areas, epidemiology and projects relating to the diverse problems of health delivery system. The selection of epidemiologic studies, of course, depends upon the expertise, enthusiasm and degree of interest among the faculty of the department but all programs share one common thread of cohesion. The objectives underlying this heavy emphasis on epidemiologic research are obvious. The application of our medical skills to the underlying causation of disease in the community provides the practicing physician with a tool to the understanding of the causation of disease process and, more specifically, the tools to institute preventive programs.

In the Department of Community Health at Davis, we have emphasized two specific forms of epidemiologic inquiry. One rather basic form attempts to define and describe epidemiologic phenomena associated with such community health problems as hypertension, stroke, coronary heart disease, infant sudden death, spinal cord trauma, and injuries from motorcyle collisions. This particular research endeavor concerns itself with the application of basic epidemiologic skills to such complicated and enormous problems as the prevention of coronary heart disease, hypertension and stroke. In these situations, our current activities are focused on research to ascertain the effect of intervention in risk factors contributing to these epidemics. The second field of activity and research in our department involves the problems of health care delivery. We have attempted, through community health surveys, to construct stochastic models, development and testing of evaluation criteria, evaluation of ongoing concepts and advances in health care delivery to broaden our perspective of the understanding of the system of health care delivery, but with a principal focus on the application of epidemiologic skills to this multidimensional, complex issue.

Refer to: Ward PD: California Regional Medical Programs. *In* Community Medicine in California—A Symposium. Calif Med 118:88-90, Apr 1973

California Regional Medical Programs

PAUL D. WARD

AMONG THOSE WHO LABOR in the healing arts, the term *community* medicine may be subject to as many divergent descriptions as the proverbial elephant defined by a team of blind men. From the viewpoint of Regional Medical Programs, however, community medicine focuses on provision of personal health care services to those deprived of services, after strong and continuing community involvement and advice in the creation of the services. Community medicine thus attempts the improvement of health care through extension of modern medical practices in a manner that is readily available, accessible and acceptable to the patients who are without adequate care.

The California Regional Medical Program became actively involved in community medicine as the national Administration's goals transferred attention from emphasis on categorical diseases toward improvement in the health care delivery system and in the recruitment and training of the manpower pool available to provide care. Changes in program direction are reflected in the recently revised statement of objectives for the California RMP:

". . . Although the California Committee on Regional Medical Programs believes that the categorical disease emphasis is still a functional approach to solving problems of access to care, it recognizes that a categorical approach *alone* may not be expedient where care is not readily available."

Later, the objectives statement describes medically underserved families and groups needing particular attention:

". . . High priority shall be given to programs that will benefit target groups with special needs. These include the urban and rural poor, American Indians and other disadvantaged minority groups, migrant farm families, children during the first five years of life, and women of child-bearing age who cannot presently obtain family planning services."

While these are high priority needs, others are not excluded in the RMP efforts to develop community medicine programs combining quality of care with community involvement and participation in the planning and developing of services.

The California Regional Medical Program is charged with providing a forum to "improve the medical care to the citizens of California." Problems exist in every type of community within the state—from Watts in Los Angeles to the isolated northeastern counties. In a state with roughly 10 percent of the nation's population, virtually every kind of ethnic community is represented. Solutions to the problems may vary considerably, shaped according to the expressed needs of the community to be served, but a common theme binds them together. The health care services resulting from community participation and planning are based on what the recipients believe to be the availability, accessibility and acceptability of the services and, particularly, the appropriateness of the services offered. These four "A's" are essential parts of the national Regional Medical Programs Service guidelines to "the elements of the process of regionalization." These seven elements are involvement, identification of needs and opportunities, assessment of resources, definition of objectives, setting of priorities, implementation and evaluation.

Programs in community medicine must obviously rely on the wisdom and experience of the health care providers who help stimulate and advise community representatives and, once the programs are under way, provide care. Quality of care has traditionally been a major concern of providers; it is also uppermost in the minds of the recipients, no matter what their lifestyle or background. Quality of care, however, may not deliver its full promise unless it is made a part of a coherent, structured system incorporating coordinated access to secondary and tertiary care, and insuring accessibility to primary care, adequate emergency services, preventive services including health education, and moderation of medical care costs. Considerations of quality care alone suggest that community medicine cannot confine itself to the needs of the poor and minority groups, great as the barriers to good health services are for them. All city residents, regardless of income level, need an effective emergency care system. Many

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rural communities have little or no emergency services to rely on. It is not the poor who face the greatest problem in paying for health services, but the middle class and lower middle class—those who earn too much to benefit from government-subsidized programs, but cannot afford health insurance or provider fees. These patients most need help in moderating costs of medical care. Conversely, all of us should benefit from a coherent and structured system that offers efficient utilization of available resources.

In its work in community medicine the California Regional Medical Program offers technical assistance not only for potential solutions to medical and health problems but also to locate potential funding sources outside of RMP. Thus local program staff developed a proposal ultimately resulting in a $2.5 million neighborhood health center funded by the Office of Economic Opportunity in Northeast San Fernando Valley. The California Committee on Regional Medical Programs is the temporary fiscal agent for an OEO-funded outpatient department improvement grant at San Francisco General Hospital. CCRMP staff provides grantee management functions and assistance in recruiting and training a community-based board of directors who will be expected to assume grantee responsibilities.

Examples of California programs frequently cited as models of joint provider-community involvement in meeting community needs are the development of the Charles R. Drew Postgraduate Medical School in Watts and the activities of the East Los Angeles Task Force, operating in a Chicano barrio of Los Angeles.

Individually-tailored activities, ideally, govern RMP program staff efforts. For example, in Ventura County a project would integrate all provider eligibility, billing and reimbursement needs into a coordinated system moderating the costs of health care. Improved bookkeeping will, it is believed, encourage physicians to accept more low-income patients. Meanwhile people hired from the community and trained as health agents will help to make the local delivery system better understood and more accessible and acceptable to the community. Access to health care in metropolitan San Bernardino-Riverside would be provided for Indians on reservations, the elderly and other underserved groups through a medical transportation system designed to make the best use of available resources.

In Los Angeles County three California Area Offices are joining in development of a county-wide emergency medical services system, through coordination of all organizations involved in emergency services and through training for both paraprofessionals and physicians.

Categorical activities are also effective in serving community needs. A comprehensive dental health project in Ventura County will provide care for disadvantaged children otherwise ineligible for services and a dental health education program to be included in county schools' curricula. In Watts a volunteer program in stroke rehabilitation, resocialization and prevention is developing additional manpower resources for helping these often-neglected patients, and at the same time is developing in the volunteers who undergo training a talent for helping to alert the community to local health care needs.

Community health problems can be lessened through direct involvement of providers. A developmental component project has helped to introduce providers at Mount Zion Hospital in San Francisco to the differing lifestyles of minority patients in order to reduce sociocultural barriers to effective care. A related project, operated through the Golden State Medical Association, is evaluating health care services provided by Black physicians in urban ghettos of San Francisco, Sacramento, Fresno, Los Angeles, San Diego and Oakland, in a search for potentially improved methods of providing care. In still another project 60 practitioners are being trained to assist physicians in providing service in underserved urban and rural areas.

Community involvement in the solution of health care problems can be enhanced by patient-oriented health education programs. One of the earliest in California, at Roseville, employed multiphasic screening to stimulate health need awareness and responsibilities. In the Redwood Empire, cardiopulmonary resuscitation training was provided first for a cadre of rescue workers who, in turn, trained an additional 2,000 community residents. In San Diego an emphysema club exemplifies categorical activity. In Orange County one project focuses on a specific problem of a retirement community—myocardial infarction. Another, the Community Referral and Information Service, helps to coordinate the use of existing health resources. The Firebaugh-Mendota pro-

gram, which has received strong support from the California Medical Association, will train a community board to plan and implement a comprehensive rural health care delivery system. The highly successful *Tel-Med* provides wide-ranging patient information through toll-free telephone calls. On the Morongo and Soboda Indian reservations young Indians have been trained as health educators. The Drew School sponsors community health committees and youth groups, dealing with problems ranging from obesity as a health problem and barrier to employment to those of drugs and venereal disease. In East Menlo Park, Black medical students are training volunteers to implement a screening and counselling program for sickle cell anemia. In Santa Maria Valley, farmworkers are being trained to provide dental health education and referral services to families.

Access to primary care is often a major need, whether a community is an isolated rural area or within a large city. In northern San Mateo County family-centered home health care will begin to be offered in a model system developed through Our Lady of Guadalupe Clinic, funded by RMP, serving families whose cultural and economic background has been a barrier to obtaining health care through traditional channels. Local community groups and the San Mateo County Board of Supervisors, along with RMP, are committed to the support of the developing system.

In Los Angeles primary care is available for a large group of urban American Indians who developed a community clinic, with RMP assistance, to serve their own needs. The Indian clinic is part of the Southern California Council of Free Clinics, whose 33 members share management, administrative and other skills that improve utilization of community involvement of volunteers and resources. Primary care, laboratory tests and patient education are offered in Riverside County minority communities through a mobile clinic.

Primary care is being provided in Humboldt-Del Norte Counties to Indians living in the Coast Range; health aides have been trained; a medical-dental clinic has been established, served by local providers, "flying samaritans," and volunteers; referral and transportaion services have been set up. The project is supported by RMP, the United Indian Health Service, the California Rural Indian Health Program, Student American Dental Association, local volunteer agencies, and County and State Public Health Departments.

A related demonstration project in northeastern California will test several rural delivery models, in each of several counties using different combinations of nurse practitioner, physician's assistant, triage person or other allied health professionals teamed with an MD.

Many of these activities, which are by no means all-inclusive of the community medicine-based efforts of the California Regional Medical Program, include formal manpower training components emphasizing the establishment among minority students of new or improved skills to serve families previously deprived of primary care services.

Community medicine involves planning, provision for delivery of services, patient education, manpower training, categorical activities, virtually all major aspects of the health care delivery system. Community medicine, in the RMP view, also involves every type of community and socio-economic group, linked by the common thread of strong community involvement, in partnership with the providers in the development of services, from the moment they are first proposed. Although community involvement, in these ways, may be a source of distress to some providers who are comfortable with more traditional methods of establishing medical and health care services, patients are expecting much more than they used to, are much more sophisticated about what they need and how to get what they want and, in any case, will not make use of what they do not want. To overlook community involvement in the establishment of community medicine programs borders on the frivolous.

Regional Medical Programs are committed to effective utilization of available but often scarce resources and services. Community involvement, in tandem with the providers, from the beginning, appears to offer a higher degree of patient utilization and satisfaction. Partnerships now developing among community and professional interests could lead to significantly better quality of health care available for all our citizens and a gratifying improvement in the health care delivery system.

Refer to: Guillozet N: Rural medicine—Making it now, and the problems ahead (Community Medicine). Calif Med 118: 91-93, Apr 1973

Rural Medicine

Making It Now, and the Problems Ahead

NOEL GUILLOZET, MD, *King City*

King City, California, a small remote town among thousands in the nation, has demonstrated that private physicians and federal funds can jointly develop effective health care delivery mechanisms to serve residents of all incomes with a full complement of hospital and outpatient services as well as community health programs. Young health care professionals can be drawn to the traditionally difficult-to-serve rural areas. Unanswered is the problem of developing and maintaining an adequate funding base for health services in rural communities in the face of a disproportionately large number of poor people with a suboptimal job future. The dollar resources in the rural community are often simply inadequate to buy needed health and social services.

THE AMERICAN PEOPLE'S EXPECTATIONS of the medical care system have never been higher. A tide of books, articles and commentary on health care needs and an increase in health care-related legislation attest the public concern.

The issue of access to acceptable health care services is increasingly raised, more often than not in the big cities with their concentrated needs. But apart from the urban ghetto from which all persons flee who can, the cities have always been favored in the distribution of health care professionals and facilities. What of unmet rural needs as a nation sees faster progress in development of ways to pay the costs of health care for all than in assuring availability of service?

In 1973 we begin the seventh year of Rural Health Project, Inc., of King City, a collaboration of private physicians, a community hospital and the Department of Health Education and Welfare (HEW) to provide care for the region's thousand lowest-income families of the community in a "one-door" fashion in the group practice clinic and hospital used by the entire community. King City, the center of the Project's operations, is a town of some 3,700 in the lower Salinas Valley of mid-coastal California. The nearest physicians to the south are 50 miles away and the closest hospital to the north is also 50 miles. It is 120 miles distant from the closest medical center, at

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Palo Alto. A blend of patients including the low-income often Spanish-speaking migrant farm laborers who once had to travel 25 to 85 miles north to the county hospital, suffering loss of wages and long waits, to receive care for themselves and their children, now receive the same kind care by the same providers as do the people who are fully able to pay. In addition to the medical services provided by the physicians and hospital, the Project provides dental services, transports patients from all sections of the Project area when personal transportation is unavailable and provides outreach community health services through community health aides and public health nurses.

The Right to Physicians

A Community Issue

Currently 27 percent of Americans live in rural areas and towns of less than 2,500 population. In the breadth of the United States there are millions of people who live more than 100 miles from a major city, and for a number of towns of 4,000 or more there will probably be no physicians available in the 1970's unless the Federal Government devises a large-scale assignment of federal employed physicians to these areas. Some glimpses of the future are seen in a prototype National Health Service Corps which has assigned a small number of physicians and other health providers to a few communities soliciting them in California and elsewhere.

In many of the nation's towns with populations under 5,000, physicians now practicing there will not be replaced when they die or retire. For many such towns improved access to medical centers in nearby cities has done much to obviate the need for physicians of their own. When a 30-minute ride on a superhighway will reach the best in contemporary care, many communities accept the reasonability of losing their physician. Can a rural area expect a physician to voluntarily enter practice there in this decade? If a community offers only conventional rural practice conditions with unending around-the-clock calls and neither the benefits of the hospital-laboratory complex nor physician companionship, it can probably expect not to have a doctor. It is in those communities where there are no reasonably accessible sources of patient care that the want of a physician poses the greatest threat to community well-being. Emergency medical care services that depend on helicopter transport and rapid ground transit overlook fundamental problems. Helicopters are scarce and costly and the country is very big; ground transportation by rapid transit, apart from high-speed highways, has not even been accepted as one of this decade's priorities.

Small Town Practice

The Unusual Example

There are some small communities that may point the way to meeting future rural health care needs by means other than federal physician assignment.

King City with its Rural Health Project, Southern Monterey County Medical Group, and George L. Mee Memorial Hospital provided nearly 55,000 doctor-patient contacts in 1971. King City serves a surrounding rural population of approximately 22,000 plus seasonal migrants scattered over an area twice the size of Rhode Island. It is able to recruit young physicians at a time when other large towns nearby are failing to replace their aging and retiring practitioners. The secret?—modern group practice of all area physicians with the innovative use of the most modern paramedical personnel to aid in house calls, home care of the infirm, well child pediatrics, an increasingly heavy obstetrics load, and programs of medical outreach and community health.

Six family practitioners are backed by a board-certified general surgeon, board-certified pediatrician and a radiologist as full-time members of the group. On schedules varying from twice weekly to bi-weekly, an orthopedic surgeon, urologic surgeon, ophthalmologist, dermatologist, and two otolaryngologists see patients in the group's facilities and perform elective and emergency operations as well as diagnostic procedures in the adjacent community hospital. The group's pediatric nurse practitioner, obstetric nurse practitioner, physical therapist and history takers further expand the efforts of the group's physicians. Another unique aspect of King City is its community mental health services. Usually rural areas distant from major cities have little or no access to psychiatrists, psychologists or other professional mental health supportive personnel. King City has two psychiatric social workers incorporated into the group practice, who for three days a week provide counseling to community members in a program supported jointly by the Monterey County Health Department, the medical group, and the Rural Health Project.

Good Planning

The Doctor and Hospital are Neighbors

Good planning has placed a modern medical group adjacent to a contemporary community hospital with 44 beds and intensive care unit. The proximity permits physicians to check frequently on the more seriously ill patients in the hospital. Seven of the group's physicians live within three blocks of the clinic-hospital complex. For each of the five weekdays, physicians take turns serving for an on-call 24-hour period so that the others may maintain patient schedules free of distractions and free nights, while providing 24-hour a day emergency care to residents of the area and travelers. Physicians by turn rotate one week-end of call each two months to meet community needs and to allow the freedom from constant on-call responsibility that so often proves unbearable to solo rural practitioners.

Rural Physicians and the Medical Center

A Rare Partnership

Stanford University Medical Center, 120 miles distant, has strong bonds with King City and on alternate weeks sends clinical visitants in cardiology, neurology, rheumatology, and other medical subspecialties. A recent direct-line transmission system between King City and Stanford provides 24-hour a day cardiologist consultation and electrocardiograms can be transmitted instantly from the hospital in King City to Stanford for advice on dealing with acutely ill patients. Through the group's sponsorship of the Regional Medical Program and the Stanford affiliation the group has monthly visits from guest lecturers on postgraduate medical education topics of clinical medicine and care delivery for physicians scattered throughout Monterey County. The group offers a clerkship in health care delivery to the community for sophomore and junior medical students through Stanford's Department of Community and Preventive Medicine. Not only is this a teaching opportunity for group physicians, it is an unusual opportunity, too, for students to work alongside the group's new direct care providers—pediatric nurse practitioner and obstetric nurse practitioner.

Problems Ahead

The King City example has effectively demonstrated that by serving a larger population through group practice and an unusual complement of supportive services a town of 5,000 people can attract and keep health care professionals in a traditionally difficult-to-service rural area. King City with its existent health care resoures is vastly ahead of those rural communities that must face the issues of willingness and ability to pay the generous start-up costs and even greater continuing costs of a modern and acceptable health care delivery system. Facing the Salinas Valley and hundreds of other communities throughout the nation are the intricate and related and economic problems generated by the further mechanization of agriculture and diminished number of jobs. Intensive farming of such new valley enterprises as mechanically cultivated vineyards directed by distant corporate structures will reduce the numbers of laborers and leave only land rentals and the wages of a few workers to buy services and goods in the community. The profits flee, leaving to the federal and state governments, when they choose to assume it, the burdens of redistribution to the rural areas of profits through the tax dollar as subsidized housing, schools or health care.

In the shorter term, the Rural Health Project and its recipients face the uncertainty of federal willingness to pay the costs of providing health care services for the poor in that interim period between existent program funding and the acceptance of one of the more sweeping proposals for national health care insurance yet to issue from the drawing boards in an acceptable fashion. The Department of Health, Education and Welfare, the principal funding source of care for the "working poor" who do not qualify for welfare subsidies, has faced increasing difficulty in obtaining requested funds. Confronted with a national cost spiral for all goods and services, diminished funds can only buy fewer services. Increasing efficiency multiplies some health care dollars, but ultimately services must diminish.

The King City community, like many others has cheerfully and guiltlessly solicited and accepted or anticipates funds for a city park, municipal sewage systems, landing lights for a nearby airfield, a major highway, migrant housing and a score of smaller but rapidly multiplying subsidies. America endures few retrenchments in meeting its social needs. Good medical care is the most recently recognized and demanded of social services and neither expectations nor demands made have ever been higher. Perhaps we should look as optimistically to extended federal support for a large share of rural health service costs as we do for other community activities and responsibilities.

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Ghetto America and Developing World Health Care Delivery

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THE HEALTH CARE DELIVERY SYSTEM in ghetto America is being questioned as never before, for two principal reasons. One is the imminence of a national health insurance program which should make first class health care financially available to the medically deprived. The second is the militancy of the ghetto members who are demanding improved health care now.

Plans have been implemented to increase the number of physicians, health workers and hospital beds, but these measures offer incomplete solutions to the complex problems of ghetto health care. Simply supplying more facilities and personnel is not enough. Furthermore, programs imposed from without lack relevance to the ills they are intended to alleviate, so it is essential that programs designed to improve the health of the ghetto residents follow studies done on comparable models or from within the ghetto itself.

Professionals in the field of international medicine have long been at work to bring improved health care to the two-thirds of the world which toward solutions for the people of the developing world.[1] These studies suggest that the health care remains medically, economically and educationally deprived. Men such as John Bryant have identified the critical health care problems and worked problems and solutions of the developing world may well serve as models for initial phases of health care improvement in ghetto America.

Carl Taylor of Johns Hopkins Medical School has emphasized the relevance of lessons learned overseas in meeting problems at home. After two or more years in a developing country, most of the physicians trained in his international health residency program return to the United States to meet the primary health needs in our country. Now working in the inner-city programs of Harlem, Washington and Watts, in Appalachia and on Indian reservations, they are applying the lessons learned abroad in improving organization of comprehensive health services, reducing cost of medical care and instituting family planning.[2]

Before dealing with the similarities in health care in the developing world and ghetto America, however, we must recognize two significant differences. The first is a matter of degree or numbers. The magnitude of medical problems in the developing world is usually far greater than that experienced in the American ghetto. The second difference involves the level of expectations of the

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residents of the ghetto as compared with those of the developing world. This level of expectation is much higher in the ghetto because of the visibility of advanced medical care via the communication media and the proximity of affluent neighborhoods with better health services.

The similarities between the health problems of the developing world and the ghetto are both numerous and basic. They have to do first with the non-medical factors which identify the deprived peoples of the world: substandard housing and sanitation; rapidly growing population; high incidence of unemployment; rural to urban migration of unskilled labor; shortage of persons with skills needed to improve the status of the deprived community; overcrowded, understaffed and underequipped schools; discrimination and segregation; and minimal involvement in political affairs. To this list must be added the growing instability of the primary family unit and the increase in drug usage and abuse.

Medical, Non-Medical Factors

The non-medical factors which identify the deprived peoples of the world cannot be isolated from the medical factors because they closely interrelate in a life cycle of deprivation. The cycle usually starts with lack of proper care during pregnancy, resulting in a high incidence of premature infants of low birth weight. The low income family is further haunted by poor nutrition and poor health care, which accentuate early physical and mental defects. The child's education is in turn limited by his poor health status, by the overcrowded classes at school, and in many instances inadequate motivation from his family. With this background the youngster is locked into a system of limited job opportunities. Poverty is his lot and he is forced into a new life cycle of deprivation.[3]

Because he functions in this economic, social and cultural setting apart from his privileged neighbor, the resident of the developing world and the ghetto is not often introduced into a health care system through a practitioner of modern medicine. Instead, traditional or folk medicine frequently serves as the primary and sometimes the only health resource. The extent to which cultural medicine is accepted depends on cultural patterns in the region, the educational level of the patient population, and the availability of western medicine.

The Role of "Cultural Medicine"

Cultural medicine as practiced by family elders, priests, witch doctors, sorcerers, herbalists, and acupuncturists who are not physicians is scorned by professionals in western medicine. Yet the supportive role played by these traditionalists serves to meet many of the anxieties and concerns generated by ill health. Most of these anxieties and concerns are poorly understood by western doctors because the doctors function outside the patients' cultural milieu.

Jean Masamba, a theology student from Zaire (Congo), wrote a doctoral thesis which reveals why the physician who is not culturally attuned to his patient may have great difficulty in solving the patient's total health problem. He explains that "attempts to bring sociology and cultural beliefs into the art of healing is not easy since each practitioner confronts not only the people he is to study and cure, but also his own perceptions of of the people and his projections on them." For example a western-oriented doctor may not understand that in Zaire he cannot offer a healing service to a mother who believes that her child has fever because of a spell. If the sickness from which the child suffers is treated by the appropriate medicine, the child may appear to get well. But to the mother the sickness of the spell from which the child suffers will continue to do harm. The child can only be healed, according to the mother, by a dialogue of reconciliation with a practitioner of traditional medicine.[4]

The western doctor can learn much from cultural medicine. The primary lesson may well be that healing is a multidimensional phenomenon which includes not only the classical psychosomatic factors, but also the ethical and cultural elements of the patient's life style. A multidimensional approach may be one of the keys to success in ghetto health care delivery. Translators must be found within the ghetto who can interpret the ethical and cultural needs of the ghetto residents to those delivering medical assistance. These translators will also function to reassure the ghetto community of the role which will be played by the the outside professionals. Communication with the ghetto is essential, but equally important is the need to train health workers to perform effectively outside the sphere of an upper middle-class socio-economic pattern from which most of today's health workers come.

Guiding Toward Health Care

The introduction of the patient into the health care system through the neighborhood or village practitioner need not mean primitive health care if the patient has mobility toward advanced health care. But in both the developing world and ghetto America, a high incidence of such medical problems as fetal mortality, maternal mortality, tuberculosis and nutritional deficiencies reflects the fact that most of the patients lack mobility and are arrested at a primitive level of health care.[1,5]

Protein-calorie deficiency diseases such as kwashiorkor and marasmus cause an estimated 12 percent of the deaths of children in the developing world. Studies in rural Mississippi suggest that there are pockets of deprivation which closely match the protein-calorie deficiency conditions of the developing world. A study of a black ghetto area in Washington revealed that maternal mortality of non-white ghetto residents was four times that of white non-ghetto residents. Infant mortality was 58 percent higher among non-whites.[1,5,6,7]

How the infant mortality rate may relate to the maldistribution of medical care is suggested in a study from Nigeria where the infant mortality rate in the major city of Lagos is reported at 60 to 70 per thousand while in rural Nigeria it is over 300. In Lagos the number of inhabitants per physician is 2,060; in the rest of the country it is 59,000 per physician.[1]

A number of reports from the United States indicate a progressive departure of physicians from neighborhoods that have become ghettos. The result has been a physician population ratio in the ghetto comparable to the ratio reported from major cities in the developing world. Poverty ghettos in Baltimore report a ratio of 1:6,600; in Watts, 1:2,600; in Chicago's ghettos, 1:1,600. This may be compared with a United States average of 1:650.[5]

The preceding statistics are somewhat sterile, for they do not deal with the question of the physician's capabilities. What is a doctor in the developing world, and what is he in ghetto America? In the developing world his training and talents vary greatly, from the medical auxiliary to the Fellows of the Royal College of Physicians and Surgeons. In America a ghetto physician type seems to be emerging. Dr. John Hollomon, a past president of the National Medical Association, has stated, "Most ghetto-based physicians are less well trained, older, see more patients, practice little preventive medicine and are more authoritarian."[8] In 1969 a study made by the Harvard Medical School Commission on Relations with the Black Community portrays the ghetto doctor as a general practitioner whose mean age is 66 years, and who in one out of two cases is a graduate of a medical school which no longer exists. In Chicago 100 doctors accounted for 70 percent of the visits paid for by the Illinois Department of Public Aid for indigent outpatient care. Sixty of these doctors had no hospital privileges. Of the five physicians practicing in the Kenwood-Oakland Community of 45,000 residents, two were cited by the Chicago Board of Health for operating an unsanitary medical facility. One of the two physicians was paid $95,729 in 1968 for treating public aid recipients and the other $87,643.[5]

The voices of the ghetto residents have been heard and reported in such studies as the "Peel Report" (Comprehensive Community Health Services from New York City. Report of Commission on the Delivery of Personal Health Services, 1967). This report calls attention to the long wait for appointments, the fragmentation of services, the abrupt and hurried treatment, the impersonal care from an overworked staff, the confusion stemming from complicated red tape, the crowded conditions and the lack of adequate medical records. To this list could be added the unsympathetic staff members who cannot bridge cultural or language barriers, the patient who fears experimentation or treatment which is not understood, the patient who is concerned with the visible double standard of medical care, and the patient who fears the hospital as the place where one goes to die.

Ad Hoc but Not a Plan

It would appear that the American non-system of medical care is at work in ghetto America. Ad hoc programs continue to be the rule rather than the exception. This pattern of health care delivery has been described as "a bewildering essentially scatterbrained kind of business, expanding steadily without being planned or run by anyone in particular."[9]

It is clear that because of its complexity a comprehensive plan is needed to meet the health care problems of the ghetto. A definition of this comprehensive health plan must be found by a study of the ghetto resident in his immediate social

environment. Investigators must listen to the ghetto residents to determine their priorities. This can be done most effectively by living and working in the ghetto to learn from the residents those aspects of life which are unteachable in the conventional educational manner.[10]

These are the lessons which have been learned by those who are revolutionizing health care delivery in the developing world and the ghetto. The transplantation of western medicine in the form of an isolated hospital or clinic has done no more to solve the overwhelming health care problems of the people of the developing world than of the residents of the ghetto.

In our own country quite as much as elsewhere in the world, the solution to the health needs of the deprived peoples must come through on-site evaluations, the use of local resources for long range planning, and the introduction of the patient into a health care system that allows for upward migration through progressively advanced medical systems that emphasize the optimum use of available trained personnel and facilities.

Summation

A close relationship exists between the primary health care problems of the developing world and the ghetto or poverty communities in the United States. There are differences in degree or numbers, but these differences should not alter the applicability of lessons learned from successful programs in primary health care in the developing world. Dr. Maurice King, editor of a symposium entitled *Medical Care in Developing Countries*, outlines 12 major axioms on medical care in poverty regions.[11] These have been integrated with information which has already been presented in this paper to establish ten basic concepts for primary health care delivery in a ghetto or poverty community:

1. Health care solutions for the ghetto or poverty communities must be developed from a direct evaluation of their health needs and resources. Because of pronounced differences in culture and human and economic resources, preconceived notions of health care as established in non-poverty communities must frequently be modified when applied to ghetto and poverty areas.

2. Methods must be adapted to the patterns of the existing culture. Traditional and folk medicine must be recognized and understood. Folk medicine which is innocuous can be passively accepted while cultural medicine which may result in additional trauma to the body and delay in treatment must be vigorously attacked with effective health education.

3. Primary health care must be effective but not necessarily comprehensive so that therapeutic and economic efficiency is achieved in the treatment of most common conditions.

4. Primary health care units should be close to the patient's home so that some form of basic medical care is available at all times to all the people.

5. The health care system should be expanded as funds and skills become available and as health education improves patients' understanding and acceptance of advanced treatment techniques.

6. Until the doctor-patient ratio is improved, auxiliaries will play a most important role in health care delivery and education. The health care system should be constructed so as to allow for the mobility of the more seriously ill patient up the ladder of medical care. In this way, the talents of the few physicians and other health care specialists will be used more effectively.

7. Health care professionals must share the power of policy-making with the residents of the community served.

8. Financial or economic benefits must also be shared through maximum employment of residents from the ghetto or poverty community.

9. The medical services must allow for upward mobility of staff and progressive improvement of the quantity and quality of medical care delivered.

10. Improved health care is only a part of a total effort necessary to elevate the status of ghetto and poverty community residents. Those who work in the health field must be cognizant of the need for housing, education, and economic improvement as vital to the cause of securing human dignity.

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Health Care for a Rural Minority

Lessons from the Modoc Indian Country in California

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RURAL AREAS AND MINORITY COMMUNITIES each present distinctive problems in health care delivery. In some parts of California the two combine to present new problems unique to their combination. One such area is Modoc County, where I participated in a preceptorship in community medicine during the summer of 1972, in the service of the Modoc-Lassen Indian Development Committee.

Modoc County is a relatively large (6,000 square miles), thinly populated (7,800) area in the extreme northeast corner of California. It is possibly the last remnant of true frontier left in the the state. Modoc was settled very late, in the 1860's, and has retained many of its early pioneer characteristics. Its economy is based on cattle ranching and timber, it possesses abundant open space, and it has a relatively large proportion of Indians in the population by California standards (3.2 percent). The times since have not been especially kind to Modoc, as is shown by the steady 1 percent a year loss of population since 1950, a demographic decline unique in California.[1] Indians are by a wide margin the largest minority group in Modoc, where they occupy the lowest rung in the socioeconomic ladder. By whatever standard, be it income, housing quality, cultural expression, or self-determination, the quality of life for Indians is considerably below that of the majority population.

It is hoped that by examining the extreme case of Modoc County, a focus of attention can be brought to problems common to rural and isolated areas and rural minorities. In addition to examples drawn from Modoc, experiences in other areas, such as Lassen, Los Angeles, San Bernardino, Monterey and Kern Counties, Mexico, and rural districts of Nevada, Arizona, Oregon, and Hawaii contributed to the development of conclusions presented here.

Health Care and the Rural Minority

Rural areas are subject to a pattern of health care problems distinct from those of more populated areas. These problems are perhaps best examined by a "systems review" of the health care system itself and its context, with special reference to the implications of these problems for minorities.

Environmental Health

Environmental health has specific dimensions in rural areas, related most often to water quality, housing quality, and specific, focal problems arising from the local economic profile (such as pesticide use, stationary sources of emissions or effluents, and groundwater contamination) rather than

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the complex of environmental insults characteristic of urban areas. The problems of environmental health typically affect the indigent of an area most severely, since they lack the means to escape or correct the situation. This has been repeatedly recognized for urban communities but it is equally true for rural areas.[2] In 1967, Carl Overmier, then Modoc County Sanitarian, remarked, "Few people in this day and age can begin to imagine that families are living under such deplorable conditions as exist among Indian families in Modoc County. . . ."[3] These conditions are only now being substantially improved. It is small wonder, given that the basic housing unit of the Indian family in Modoc is a wooden-frame cabin, poorly insulated and heated by a wood-burning stove, that hospital admissions for respiratory ailments, a leading cause of death among California Indians generally,[4] peak dramatically in the winter months and during the most extreme winters.[5] Water quality is also a problem here, and in 1963 an epidemic of gastrointestinal upset swept the Fort Bidwell area, followed by an effort by authorities to decontaminate the water supply.[5] The medical profession in Modoc County has documented problems of environmental health in an attempt to stimulate action on these problems.[6] In general, however, whether it be in rural or urban areas, the medical profession as a whole has played a very self-limiting role in the environmental health of human settlements, acting to keep conditions tolerable instead of optimal.[7]

Safety

Work-related injuries reflect the relatively high-risk occupations of rural economies (ranch work, road construction, sawmill operation). An unskilled or semiskilled minority member cannot move freely into a less hazardous job. More, some of the most hazardous jobs—fire-fighting, for example—are attractive because they are the most lucrative. Traffic conditions are frequently made dangerous by commercial vehicles (agricultural implements, logging trucks), wandering large animals (deer, horses, and cattle), road hazards (long monotonous stretches, hairpin curves), and inclement weather.[8] The rural indigent, as well as his urban counterpart, is likely to rely on an older automobile for transportation, typically sharing the vehicle among family and friends. He is often unable to afford the expenses of keeping it in proper and safe running order. Where alcoholism is a factor, all of these safety problems become exaggerated and the number of violence-related injuries increases. This is especially true where a deep undercurrent of hostility accompanies the problem of alcoholism, as in the Indian community.

Economic

Consumer practices in rural areas are similar to those of urban areas, since both are subject to the same advertising and share communications. Food prices are often relatively higher in rural areas (sometimes even for goods locally produced) and the number of merchants available for comparison shopping is limited. Substitutions in diet are not made easily, especially when an increase in cost is involved, and attempts to correct the severe dietary problems of the Indian community have predictably failed unless accompanied by consumer education. Indian men in Modoc are generally employed in seasonal jobs. Summer earnings must support the family all year in an economy with few alternative occupations. Unemployment is particularly threatening to the Indian community. The human toll of long-term unemployment and meaningless inactivity has been called "an unprecedented mental health problem" entailing a professional obligation for involvement by psychiatrists and mental health authorities.[9] Certainly the Indian community shares the general problems of the American rural poor, with all that those problems imply for health care delivery.[10]

Emergency care

Emergency care is a major problem in rural areas. Isolation and long distances make emergency care delivery difficult. In the city normal circulation of people, neighborhood observation, and continual monitoring by police and fire departments bring most emergency problems to the attention of authorities fairly promptly and emergency care is usually minutes away by ambulance or private car. Rural districts have no such circulation or established monitoring systems throughout much of their areas. If an accident does not occur with others present or on a major patrolled highway, the victim will remain untreated unless he is fortuitously discovered or sufficiently conscious to seek care himself. Once the emergency is known, ambulance service is often inadequate or unreliable and the distances to primary care excessive. The expected increase in mortality and morbidity when accidents occur in rural rather than urban areas is confirmed by survey data.[11] The

Superior California Comprehensive Health Planning Association, which includes Modoc, is preparing to develop and test the feasibility of a system based on centralized emergency care facilities and advanced ground and air ambulance services with on-board life support systems.[12] Consideration has also been given to utilizing local former nurses for volunteer, emergency services when the need arises in this area.

Non-Emergency Care

Elective visits to a physician, for routine examination or discussion of a particular problem or question are logistically difficult in thinly populated areas, both because of the distances and because arrangements must often be made to cover employment and chores, with additional hands not always available. The physician may be hard-pressed to take care of his ill patients and there may be few physicians nearby for alternate selection. The patient may therefore be subjected to a long and uncertain wait; a routine visit to the doctor may represent an investment of an entire working day. Unless one is unemployed and without children, this imposes great hardship.

There are three physicians in Modoc County, one located some 25 miles from the other two (via a road which may be impassable at times during the winter). The isolated physician sometimes takes patients until 3:00 a.m., by which time they have been waiting many hours, and he is nearing exhaustion. No such discrimination occurs in Modoc, but in some other areas Medi-Cal patients are taken after paying patients or are turned away entirely by many local physicians.

Indians requiring chronic care that is not adequately supplied by Medi-Cal, or who wish elective treatment, must be transported more than 200 miles to the Indian Health Service Hospital in Schurz, Nevada. Patients served by project health aides in Susanville, Lassen County, are routinely transported 100 miles for dental care provided through the Modoc-Lassen Indian Development Committee (MLIDC) or to Schurz for programs such as diabetic clinics. Patients living close to the state border find nearby out-of-state physicians and hospitals very reluctant to accept Medi-Cal patients.

Outpatient medical services, with routine multiphasic screening and regular clinics for common chronic disease patients have been proposed for this area. The plan is to relieve the burden on both local physicians and patients through the use of a physician rotated between the two counties.[13] It has been suggested that dentists assume a larger role in some screening functions,[14] a realistic concept for the Indian community especially. Beginning in July of this year, the MLIDC will be staffed with a physician from the National Health Service Corps.

Recruitment into the Health Care System

Recruiting patients into the health care system hinges on both the accessibility of primary health care and the degree of community education regarding its use. The rural minority faces pronounced disadvantages even when such care is at hand. Recruitment requires knowledge of the services available, an understanding of their potential for cure or relief, and awareness of the need for patient cooperation in treatment and monitoring progress. What may be overlooked in recruitment are requirements for establishing confidence in the health care system, expediting access (as by providing transportation when necessary), conveying some impression of what the patient may anticipate, advocacy on behalf of the patient to ensure satisfaction of needs, and persuasion and comprehension of the system in the patient's own cultural terms.

A rural minority is likely to be both most in need of such education and least likely to draw or accept it from the channels that serve the majority. In the case of Indians, there may be suspicion and even outright hostility to recruitment into the health care system, an attitude derived from a history of deception and neglect. Indigenous health aides can play a substantial role in meeting these problems, as discussed below. Although the concept of "mainstream medicine for all Californians," implying a single route of access to high quality medical care for all,[15] may be an admirable ultimate goal, minority groups such as Indians may be better served in the near future by alternate routes of access consistent with their culture and community needs.

Physician Deployment

Rural areas lack the professional attractions to draw physicians competitively. They cannot offer, for example, access to major medical centers and postgraduate educational opportunities. More, they do not have a sufficient number of physicians to permit arrangements for time off and distribution of the patient load. These disadvantages are only incompletely balanced by the attractions of rural

life to individuals weary of congested urban settings. Health professionals who would serve minority groups often find even fewer attractive community resources. The benefits available under the National Health Service Corps may help attract physicians to remote areas of high need, but still do not match the enticements of ordinary practice and will not alleviate more than a fraction of the need.

One approach to improving professional conditions in Northern California is being developed by a project at the University of California at Davis, supported by the Regional Medical Program, which will offer rotating services, personnel in training, and educational programs over a wide area.[16] Similar programs in other parts of the state are generating a body of experience which will be invaluable in designing future projects.[17] Improved medical communications that will make efficient consultation readily available will also help.

Maintaining and building high-quality medical facilities is very difficult for rural areas. Modoc County has two hospitals, in Alturas and Cedarville, which are administered jointly as the Modoc Medical Center. The county spent $719,882 in 1971-72 to operate them, which came to about $675 per admission or a burden of $92 on each county resident.[18] This is more than twice the burden on each resident of adjoining Lassen County ($40) with a population of 22,000.[19] That costs per capita would be higher for small counties in general would seem reasonable, since few or no private facilities distribute the patient load and smaller hospitals must provide a basic minimum of equipment although they may be unable to obtain economies of scale. Further development in extending medical facilities might logically emphasize outpatient and emergency care clinics with efficient, rapid, and subsidized ambulance transportation to larger hospitals serving entire regions.

The primary problems of rural health care can be summarized as a triad: distance, density, and delivery. A useful model for the reconstruction and reintegration of health care systems may be that proposed by Anlyan.[20] In his scheme, time-availability becomes the critical concept: Dire emergency care should be available within 15 minutes, trained emergency care personnel between 15 and 30 minutes, primary physician care within an hour, secondary specialty care within two hours, and tertiary subspecialty, university medical center, or equivalent care within five hours. This proposal calls for nothing less than the coordination and articulation of all tiers of medical services, from the citizen with some skills in first aid to the most expert medical intervention. In an era of rapid and efficient transportation and communications, this is not unrealistic as an eventual goal, especially since "care" may not necessarily imply the the physical presence of the physician if the situation can be handled by remote monitoring and direction of local personnel.

Special Problems of a Rural Minority: the Indian in Modoc

The Indian has been subjected to a variety of experiences contributing to a discouraged and skeptical attitude toward the majority health care system. For the older generation especially, the physician is not necessarily the first in the hierarchy of resort, and the hospital is perceived as a place in which to die. Western medicine fails to provide the close support and attention that native treatment provides, and seems determined to alienate the patient from his family, his land, his culture, and all the other sources from which he draws strength. By many patients, especially the older ones, hospitalization is seen not as a step toward cure but as the final step to which the doctor resorts when things have passed beyond his power.

The Western-trained physician fails to perceive or diagnose illnesses which are very real to the Indian, or places great emphasis on disease which is neither discomforting nor disabling. A patient who is very poor and very tired, and who in the course of a discouraging life has suffered pain routinely and who has followed generations in this lifestyle is not likely to become profoundly upset when told that he has a degenerative disease which may kill him in ten or twenty years. Pain is not reacted to hysterically, and an Indian patient will sit quietly for hours before an appointment, suffering agony that would never be tolerated by the ordinary patient. In general, to an Indian pain is far less frightening than disability.

Privacy is critically important, and may become a substantial obstacle to communication with the patient. Indian communities are typically small and close-knit but may be subject to explosive internal tensions and divisions as individual frustrations and threats to the community as a whole accumulate. This and a strong sense of personal

pride make it very painful to reveal one's private affairs, and very dangerous to allow anything personal to come to the attention of opposing factions in the community.

The proper management of an Indian patient may be very different from that of a majority patient. Not only are attitudes toward health care different, but the collision of centuries of tribal experience and a discordant aggressive alien society have produced perceptions and psychic constructs that are interpretable only from within the patient's own culture. Not only are the psychological factors vastly different from those present in the majority culture, they are also very different between tribes, each of which has complicated the diversity further by developing its own introspective "ethnopsychiatric" analyses which in turn are powerful shaping factors within the culture.[21] There are also very real physiological differences between Indians and the white majority, such as the low bile acids plus lecithin to cholesterol ratios reported for bile produced by Chippewa Indian women, which predisposes to cholelithiasis, a very common disease among Indians.[22]

Alcoholism is a major health problem in Indian communities. The pharmacologic effects of ethanol offer escape from a depressing reality, release strongly inhibited behavior, and offer virtually the only form of recreation in which the individual is not expected to conform to rigid discipline. Native Indian culture was very disciplined and contemporary Indian society still places great emphasis on controlling behavior. Alcoholism has played such a major role in Indian society that it has been institutionalized as a cultural norm, a development contrary to the carefully controlled use of social and religious intoxicants among California tribes before the white invasion and the dissolution of native culture.[5]

Indians who have retained their traditional beliefs often see Western medicine as a very superficial, palliative magic which fails to perceive or deal with the profound disharmony in the universal order of things which is illness. Those who have abandoned their tribal ways still see their skepticism verified in the relatively less success Western medicine may encounter in treating Indians as compared with whites. That this lack of success may be accounted for by long neglect of preventive care, environmental risk, and delay in seeking medical attention is overlooked.

Pride is a critically important component of Indian cultures, and the typical Western disdain and ridicule of native treatment alienates many members of the Indian community, including many of those most highly educated in the Western tradition. An example of the importance assigned medicine by Indian tribes is related in the story of Ishi, the last survivor of the Yahi tribe, as he encounters and critically observes the practice of Western medicine.[23] This indiscriminate denial of an important part of Indian culture erodes confidence in Western practitioners, who appear to be ignorant of the contributions of native practice to Western pharmacopoeia, including ephedrine, curare, cocaine, quinine,[24] and (from the Indians of California) cascara sagrada.[25] These same physicians ignore the profound psychodrama inherent in "sings" and other rituals,[26] the very real manipulative skills of some tribes as in bonesetting, and the complex symbolism and significance inherent in the philosophical foundations of Indian medicine.[27] The Indian developed elaborate, internally consistent world views expressed in the naturalistic symbols and metaphors which had profound significance in his life, fused with insights obtained from mysticism and altered states of consciousness in a highly ordered fashion.[28] The white man reads these myths literally and laughs, replacing this ordered wisdom with empiricism, substituting involvement of clan and family in the health of the individual with a sterile institutional setting. Although detailed knowledge of traditional beliefs may have passed from the common knowledge of the "average" Indian, the reaction to white condescension towards the highest cultural expression of his race remains bitter and vivid.

Western medicine has largely failed to capitalize on those very patterns of belief within Indian tradition which would maximize its acceptance. Except for the Navajo-Cornell Medical Project,[29] few attempts have been made to build bridges between native culture and Western medicine. Shamanism was not an arbitrary and disorganized body of belief, although it may have degenerated to this in the hands of some quack practitioners after the white invasion. The native practices of the Achumawi, or Upper Pit River tribe of Modoc, perhaps illustrate this and typify a belief system common in Northern California.

The Achumawi shaman was admitted to practice after a long and rigorous training, the object of which was to incorporate into his own body and to learn to master and control a variety of

animate, tangible, but minute "pains" which were considered the etiologic factors of disease. The shaman's mastery of the "pain" rested in his cooperation with an interceding spirit which introduced into his own body, while he dreamed, the "pain" he would subsequently be able to cure in patients. Instruction by older shamans was deemed essential in the mastery of the "pains" and a special professional initiation ceremony admitted the shaman into practice. Surprisingly, the shamans of California did not establish organized shaman's societies, a common institution elsewhere.[30] Within a few years, the small remaining use of shamans in northeastern California will cease entirely.

Although religious missionaries had some success in translating critical elements of Christianity into native symbols and beliefs in order to promote understanding and acceptance, no such attempt was made for medicine, despite clear analogies between native belief and the germ theory of disease (and the concept of immunity). Different tribes subscribed to different belief systems, each with elements that might have been a bridge to understanding. For example, the Zuñi are reported to be skilled in massage and bone-setting, with the Hopi noted for dealing with "invasive foreign bodies," as gallstones are considered.[31] Now, the Indian has largely lost his traditional body of knowledge, but without its being replaced by a satisfactory level of health education in the Western mode. For the Achumawi, at least, this opportunity for transcultural communication in a field of intense interest to both cultures has been irretrievably lost.

Within Latin America, the problems of cultural obstacles to health care in rural areas are similar to those in the southwest United States and perhaps better understood.[32]

Meeting the Needs of the Rural Minority

The Indians of Modoc are served by a community based, health-services support organization, the Modoc-Lassen Indian Development Committee. The MLIDC offers resident dental service and a framework through which the community can deal effectively with outside agencies and individuals in matters of health. It is funded by the United States Indian Health Service through the California Rural Indian Health Board and is one of sixteen such projects. Beginning in mid-1973, the MLIDC will have a staff physician to serve its constituents in Modoc and Lassen Counties, and a clinic is nearing completion in Alturas.

In 1955, following a general policy of "termination" wherever possible, federal health services to California Indians ceased, not to be restored until 1970, by which time the situation had deteriorated badly. The MLIDC was one of nine original demonstration projects launched under state auspices in 1967.

An organization such as the MLIDC is a vehicle for acquiring and holding services for the community. It is highly dependent on outside support but depends on local leadership for policy. This makes it very vulnerable to internal divisions and controversy within the local community, but it is also a valuable means by which education occurs; the community is educated in the practical matters of agency relations and management, and outside parties are made aware of community problems and opinion. Perhaps the most valuable attribute of such an organization is its identification as being a service for the community. This is particularly important for the Indian population, since Indians do more effectively utilize services specifically identified as being for their use than they do the services that are for the entire community. Such identification is assurance of recognition of their unique problems and an attempt to provide needed services within the recipient's own culture, bypassing the cultural, linguistic, and social obstacles that seem so formidable.

Just as the MLIDC attempts to solve problems of health care delivery to the community, its staff of health aides (four for two counties) try to handle the problems of health care delivery to individuals. They are a community-based presence, transporting patients, assisting in communication between physician and patient, guiding through the maze of buraucracy, collecting survey data, representing the patient as an advocate, and regularly calling on individuals to monitor progress and need. With further training as planned, they will also be able to render some emergency care, provide health counselling, and assist in treatment. Expanding opportunities for training and job responsibilities will develop a pool of health expertise and leadership in the community, since the health aides are drawn from among the most intelligent and highly motivated in the community. At present many of the health aides are serving primarily by making available resources which are

readily available to the majority, such as transportation, articulate advocacy, and basic information.

Appropriation and administration of resources for health care programs require periodic objective evaluation of services. One procedure using hospitalization as a health status indicator was performed for the Modoc-Lassen Indian Development Committee, and is believed to be the first such evaluation for a California rural Indian health program.[5] Hospitalization data are subject to a number of limitations on use, but can be very valuable when combined with other relevant information.[33] The MLIDC survey concluded that real progress had been made since 1963 in controlling respiratory and gastrointestinal disease, diabetes, and accidents, and that much of this progress since 1968 appears due to the indirect effect of the MLIDC, which does not yet deliver medical care itself, but which filled a specific gap in the delivery of services by increasing the accessibility and conditioning the community to accept the services and utilize them effectively. It has functioned as an "accessory gatekeeper" to the health care system, recruiting and admitting Indian patients through an alternate portal of entry.

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Health Problems in the Martin Luther King, Jr., Hospital Service Area

Implications for a Community Medicine Program

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EFFECTIVE HEALTH SERVICES should result in a measurable and significant decrease in existing health problems. A careful assessment of these problems is an important initial step in developing realistic program objectives and provides a basis for evaluating progress.

There are several ways of approaching the measurement of problems, each of which has its peculiar bias. A consideration of mortality rates provides one perspective and morbidity data provides another. Both of these approaches are disease-oriented and do not provide the same insights as a study of the consumer's problems in obtaining access to care.

Simultaneous assessment by several methods increases the reliability of conclusions which are reached, but the consideration of mortality by itself can provide significant clues. This has been recognized since 1662 when John Graunt of London published his "Natural and Political Observations made upon the Bills of Mortality." Considerably more recently, and in this country, Lerner and Anderson made some interesting studies on mortality differentials between high and low-income states in the United States.[1]

Of special interest are the studies which compare, in smaller geographical areas, the mortality experience of poverty versus non-poverty populations and of white versus non-white groups. This kind of data is still rather limited. The Chicago Board of Health published a report on health and medical care in poverty areas of Chicago and showed an increased mortality related to poverty.[2] Using a more rigorous treatment of the Chicago data, Lerner presented further confirming evidence in a chapter he supplied for *Poverty and Health*.[3] Differentials in white and non-white mortality have been studied for Baltimore and Washington, D.C.[4] and Hunt and Hmyek analyzed the mortality of white and non-white infants in major United States cities.[5] Other investigators have dealt with infant, prenatal, maternal and childhood mortality in this country.[6]

This communication focuses on the area served by the Los Angeles County-Martin Luther King, Jr. General Hospital and the Charles R. Drew Postgraduate Medical School. Both of these institutions have strong commitment to effective community service and the data here described represent part of that which has been developed to provide a rational basis for establishing program priorities at the medical center. The local data are based largely on 1968 statistics and, therefore, represent the status before these institutions began rendering services.

The analysis is based on several comparisons. Because the King Hospital Service Area is predominantly black, reference is first made to the comparison of mortality rates for the white and the non-white on a national basis. Comparisons are then made with Los Angeles County as a whole and also with the West Valley Health District.

Description of the Study and Comparison Populations

The community served by the medical center is currently a 33-square-mile area located in South Central Los Angeles. Approximately 340,000 peo-

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TABLE 1.—*Age-Adjusted Death Rates per 100,000 for Selected Causes of Death, By Race, United States, 1967*

Cause of Death	Age-Adjusted Death Rates	
	White	Non-White
Heart Disease (400-402) (410-443)	263.1	310.1
Malignant Neoplasms (140-205)	126.6	154.3
Vascular Lesions Affecting Central Nervous System (300-334)	65.2	118.8
Accidents (E800-E962)	52.4	73.2
Influenza, Pneumonia (480-493)	18.8	36.4
Diabetes Mellitus (260)	12.7	24.5
Cirrhosis of Liver (581)	12.5	20.7
Nephritis and other Renal Sclerosis (592-594)	3.4	11.8
Tuberculosis (001-019)	2.2	10.1

SOURCE: National Vital Statistics Division: Vital Statistics of the United States, 1967. Vol. 11, Part A. Public Health Service, Washington, U.S. Government Printing Office, 1969.

ple (1970 census) live in this area, more than 82 percent of whom are black. Over 12 percent of the population have Spanish surnames, and the remainder are of other races. It is predominantly a low-income area with high unemployment.

For comparison, we selected the West Valley Health District, one of the 23 health service districts defined by the Los Angeles County Department of Health Services. It is a large, primarily suburban area in the northwestern part of Los Angeles County, with a population of over 550,000 people. More than 98 percent of the population is white. Economically this population is middle-class to upper middle-class. West Valley was not chosen because it is the perfect community; indeed, for some causes of death the district showed higher rates than the county as a whole. However, it is a convenient point of reference against which the King Service Area can measure its own progress toward a standard of health that is achievable within Los Angeles County. Although there are important differences between the two populations, if the King Service Area is indeed making progress, then, regardless of the reasons for the differences, the gap between the two populations should become smaller over the years.

Differences between the study and comparison areas are more than racial. The population served by the medical center is younger than that of West Valley with a median age of 23 years compared with 29 for West Valley. The median annual income (1970) is $5,950 for the Hospital Service Area and an estimated $16,000 for the West Valley area. Median annual income for the county as a whole is approximately $10,970.

White-Nonwhite Differentials in Mortality in the United States

For all the major causes of death in the United States, the rates for the white population are lower than for the non-white population, more than 90 percent of whom are black. The 1967 age-adjusted mortality rates for the leading causes of death are given in Table 1. For vascular lesions of the central nervous system, the rate for the non-white is almost double that of the white (118 to 65 per 100,000). The same is true for influenza and pneumonia, diabetes and cirrhosis of the liver. For tuberculosis, the ratio is more than four to one. The same pattern which one observes in the national data is seen to a greater or lesser extent in predominantly black urban communities. It was, therefore, reasonable to expect that one would find the same kind of problems in the King Hospital Service Area.

Differentials in Mortality Within the Los Angeles County Area

We now show how the mortality rates for the King Hospital Service Area compare with Los Angeles County as a whole and with the West Valley community. Because of the differences in the age composition of the populations, valid comparisons can be made only on age-adjusted rates. All rates are adjusted to the Los Angeles County population and the analyses are based on the 1968 vital statistics obtained from the Los Angeles County Health Department, Division of Health and Statistics. The vital statistics were provided on magnetic tape and were processed on the Univac 1108 Computers at Jet Propulsion Laboratories (California Institute of Technology).

The rates for the King Hospital Service Area conform to what might be expected in a predominantly black population. However, for heart disease—the major cause of death—the rate for the non-black population in the area is much higher than for the black population. It is suspected that a higher mortality in the Mexican-American population can be a major contributing factor since this group forms a significant proportion of the

TABLE 2.—*Age-Adjusted Death Rates per 100,000 for Selected Causes of Death—King Hospital Service Area Los Angeles County, and the West Valley Health District, 1968*

Cause of Death	*Hospital Service Area*	*L.A. County*	*West Valley*
Heart Disease (400-402) (410-443)	386.93	332.57	279.99
Malignant Neoplasms (140-205)	192.35	157.73	137.73
Vascular Lesions Affecting Central Nervous System (330-334)	132.41	101.91	103.00
Accidents (E800-E962)	75.70	53.00	42.02
Homicide (964-5) (980-99)	55.12	9.38	2.70
Cirrhosis of Liver (581)	42.52	22.55	11.97
Influenza, Pneumonia (480-493)	38.40	22.38	17.26
Early Infant Diseases (760-776)	30.20	20.08	17.70
Diabetes Mellitus (260)	28.10	12.55	8.92
Other Circulatory Diseases (451-468)	16.12	12.13	7.38
Arteriosclerosis (450)	16.07	13.04	10.38

non-black population of the King Hospital Service Area.

Comparing the King Hospital Service Area with Los Angeles County, the mortality rates for the major causes of death bear a similar relationship to the rates for the non-white and white nationally. For example, deaths from diabetes and cirrhosis of the liver occur at about twice the rate. Homicide, which does not appear among the ten leading causes of death nationally, appears in this comparison where the causes of death are ranked in order of their rates in the King Hospital Service Area. Homicide occurs in the King Hospital Service Area with six times the rate of occurrence in Los Angeles County, making it one of the ten leading causes of death. Heart disease, cancer and stroke are, as nationally, the three major killers, but death from stroke occurs at a 30 percent higher rate in the King Hospital Service Area than in Los Angeles County. Nationally the rate for the non-white is about 80 percent higher than for the white.

Comparing the King Hospital Service Area with the West Valley community, the gap is even wider. Rates for heart disease are 35 percent higher, cancer 40 percent and stroke 35 percent. Deaths from accidents occur at almost twice the rate, cirrhosis of the liver almost four times and homicide at about twenty times the rate in the West Valley community. (See Table 2.)

If one applies to the population of the King Hospital Service Area the same age- and sex-specific death rates that exist in the West Valley population, then one can calculate an "expected number of deaths." For many conditions, the number of deaths which actually occurred in the King Hospital Service Area exceeds the number which would have occurred at West Valley rates. The difference between the number that would have occurred at West Valley rates and the number that actually occurred, we call "excess deaths."

TABLE 3.—*Excess Deaths* in King Hospital Service Area Compared with West Valley Health District—Selected Causes of Death, 1968*

Cause of Death	*Number Excess Deaths*
Heart Disease (400-402) (410-443)	363
Malignant Neoplasms (140-205)	185
Homicide (964-5) (980-99)	178
Cirrhosis of Liver (581)	121
Accidents (E800-E962)	114
Vascular Lesions of Central Nervous System (330-334)	100
Influenza, Pneumonia (480-493)	72
Diabetes Mellitus (260)	65
Early Infant Diseases (760-776)	42
Nephritis (592-594)	32
TOTAL	1,272

*See text for definition.

The excess deaths for the year 1968 are shown, by cause, for the ten conditions which contributed most to the excess. These figures are shown in Table 3.

For these conditions alone, there are almost 1,300 excess deaths a year in the King Hospital Service Area. The savings of these lives provide a challenge to the new medical center.

Heart disease, cancer and homicide are the leaders in this category. Cirrhosis of the liver, accidents and stroke follow in order of importance. Based on national data, it would appear that hypertensive heart disease is the major contributor to excess deaths caused by heart disease. Among the cancer sites, cancer of the stomach, uterus, prostate, pharynx and liver contribute most to the excess. Among accidents, the excess is due largely to home accidents rather than vehicular accidents. Prematurity in the neonatal period and respiratory and gastrointestinal diseases in the postneonatal period are major contributors to the the excess in infant deaths.

The number of excess deaths does not ade-

TABLE 4.—*Person-Years Lost from Selected Causes of Death—King Hospital Service Area Compared to West Valley Health District, 1968*

Cause of Death	*Person-Years Lost*
Homicides (964-965) (980-999)	6,436
Accidents (E800-E962)	5,630
Heart Disease (400-402) (410-443)	5,149
Early Infant Diseases (760-776)	3,931
Malignant Neoplasms (140-205)	3,775
Influenza, Pneumonia (480-493)	2,650
Cirrhosis of Liver (581)	2,607
Vascular Lesions Affecting Central Nervous System (330-334)	1,512
Diabetes Mellitus (260)	902
Other Chronic Respiratory (525-526) (501-502)	868

quately indicate the priorities of attention, since the prevention of deaths at a late stage in life does not contribute as much to lengthening of life expectancy as the prevention of the same number of deaths occurring at an earlier stage in life. Therefore, we prefer to use the number of person-years lost in judging the relative importance of health problems. This statistic is derived by computing the number of excess deaths from a specific cause at each age group and multiplying it by the life expectancy at that age, then totaling over all age groups for that specific cause. Using the number of person-years lost, we obtain a different ranking of conditions. The number of person-years lost by the major causes of excess deaths are ranked and given in Table 4. This table tends to bring into sharper focus the importance of preventing excess deaths at the earliest possible age. The relationship of the major causes of excess deaths at different ages is shown in Chart 1. From these diagrams it is clear that homicide and accidents are problems of younger age groups and each death contributes many person-years lost, whereas excess deaths from cancer and stroke are largely a problem of the elderly and each death contributes far less to the loss of person-years.

The order varies from Table 3 in that deaths from homicide and accidents are shown to contribute more to years of life lost, and deaths in infancy have risen in importance as a priority on which one should focus.

Program Implications

Although mortality data do not in themselves provide a complete picture, the above findings have significant implications for program planning. Health planners often place priority on the basis of a combination of factors including severity, scope, technical feasibility and cost. If a condition is severe enough to be a leading cause of excess deaths, then it should merit the attention of those who provide health care for that population. On the other hand, we do not always have

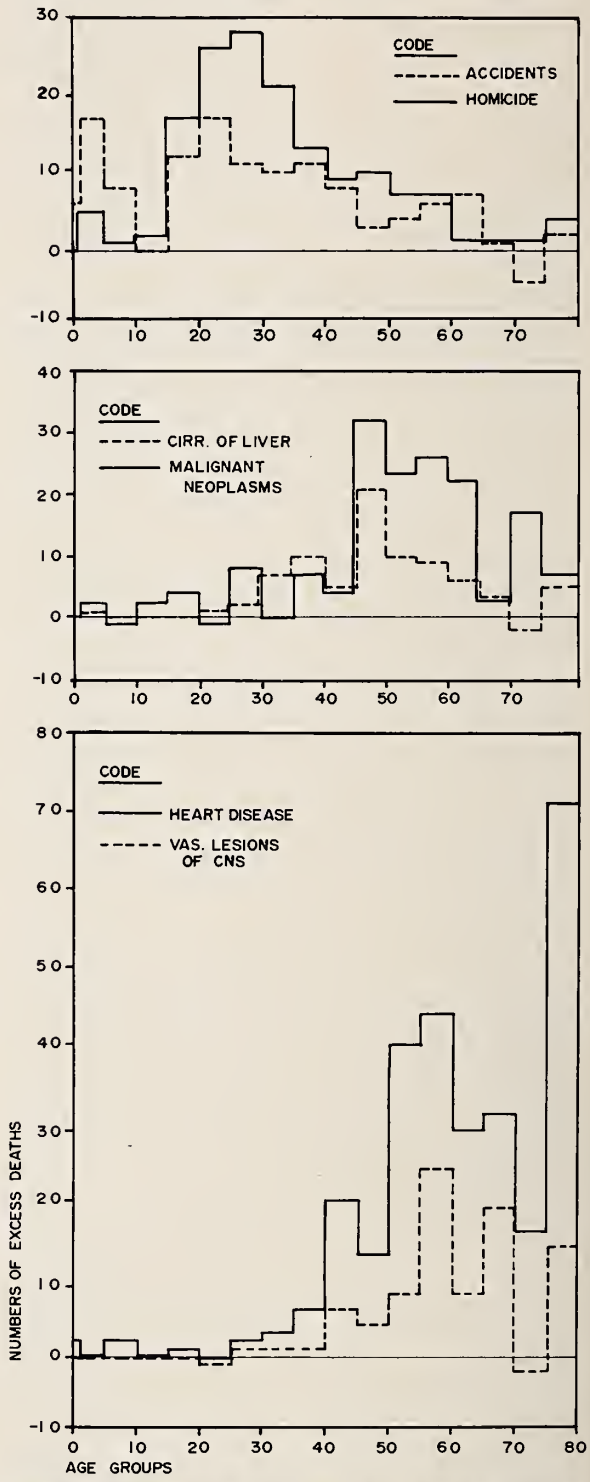


Chart 1.—Excess deaths 1968 King Hospital Service Area/West Valley Health District.

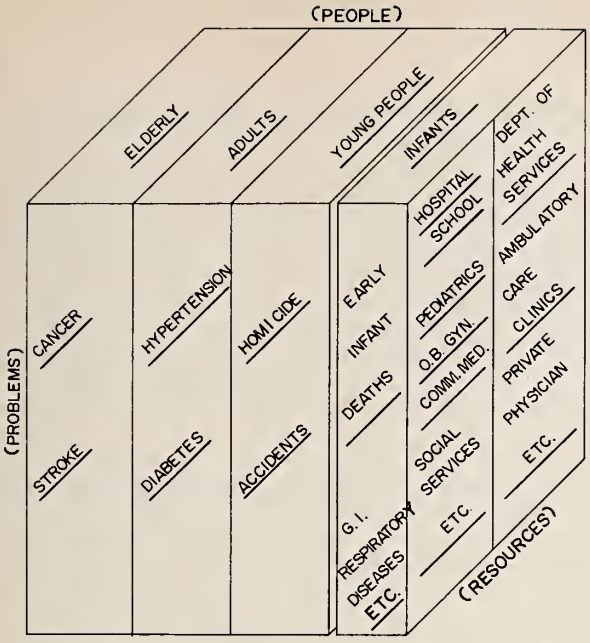


Chart 2.—Relationship among problems, resources and people to be served.

the technical knowledge or technical competence, and these, therefore, become limiting factors. Another constraint may be financial resources. With limited resources one tries to save as many lives as possible, rather than spend the same amount of money for problems which may save only a few lives.

The problems which contribute to excessive mortality present a real challenge. First of all it is immediately clear that the solutions do not all lie within the scope of medical care, but some do. For example, although our knowledge about the cause of hypertension is limited, there is perhaps still a great deal which can be done to reduce mortality by better medical care. At first it may appear futile to tackle the problems of excess deaths from homicide, yet it is possible that a significant number of the deaths may be prevented if high-quality emergency care is promptly available. Although we know socio-economic factors play an important role, we also know that excess deaths from the diseases of infancy may be decreased by improved maternal and infant care. The monitoring and thorough investigation of all infant deaths which occur in the community could possibly achieve a similar reduction in infant mortality as is achieved by the investigation and preventive conferences in the case of maternal mortality.

Narrowing the existing gap between the King Hospital Service Area and the West Valley Health District can best be achieved by the concerted effort of all services at the King Hospital and the Drew Postgraduate Medical School. It can best be achieved by an efficient organization of available resources so as to achieve the maximum benefit for the population served and, in so doing, reduce or eliminate existing problems.

For example, if one focuses on the infant population and recognizes the problem of excess infant deaths, then one can bring to bear the resources of the departments of Pediatrics, Obstetrics and Gynecology, and Community Medicine for dealing with the problem. If one decides to investigate all infant deaths, whether or not they occurred in the hospital, then this would require action on the part of the appropriate divisions of the newly-organized Los Angeles County Department of Health Care Services. An investigation of every death would involve both public and private sectors.

The approach to solving these community health problems is shown in a simplified diagram of interaction in the three dimensional model Chart 2 with the three axes representing people, problems and resources.

There is no cause of death that contributes to the excess which could not be affected by the application of our present knowledge and with commitment of adequate resources. The goal is not the elimination of death, but the achievement of a mortality status in the King Hospital Service Area equal to that which already exists in another section of Los Angeles County. To the extent that community health programs address themselves to these issues, they can be considered relevant; and the success achieved along these lines constitutes a reliable measure of the effectiveness of the health programs.

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In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BRUNING, EDWARD FREDERICK, Santa Ana. Died February 10, 1973, aged 69. Graduate of the University of Nebraska College of Medicine, Omaha, 1929. Licensed in California in 1932. Doctor Bruning was a member of the Orange County Medical Association.

CALKINS, PATRICIA HOOD, Oakland. Died February 5, 1973 in Alameda, aged 50. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1950. Doctor Calkins was an associate member of the Alameda-Contra Costa Medical Association.

CHAVEZ, MANUEL, Los Angeles. Died January 15, 1973, aged 83. Graduate of Unversidad Nacional Facultad de Medicina, Mexico, D.F., 1914. Licensed in California in 1925. Doctor Chavez was a member of the Los Angeles County Medical Association.

DATZKER, EDWIN A., Sylmar. Died November 25, 1972 of heart disease in Granada Hills, aged 46. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1954. Licensed in California in 1955. M.D. degree from California College of Medicine, 1962. Doctor Datzker was a member of the Forty-First Medical Society.

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Causes and Prevention of Failure in Varicose Vein Operations

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One hundred and one patients with poor results from the operative treatment of varicose veins were studied in an effort to determine the cause of the surgical failure. In a large majority, reoperation revealed that the primary cause of the poor result was the improper performance of the original operation. A smaller number of failures were due to errors in selecting the operative procedure. Relatively few poor results in long-term follow-up were attributable to the congenital predisposition to varicosity. When operation is properly planned and executed, it produces better long-term results than the injection compression therapy of varicose veins.

IN RECENT YEARS the value of surgical treatment of varicose veins has come under attack and the substitution of sclerotherapy as a sole therapeutic method has been advised.[3,6,14-16] Unfortunately, some of the articles on this subject in the medical literature have been the basis for distorted and exaggerated articles in some lay journals. As a result, many patients and even a significant number of physicians have become convinced that operation is of little or no value in the treatment of varicose veins.

Our experience, with careful follow-up of patients treated by a method of surgical extirpation herein described, indicates a high degree of therapeutic efficiency for this operative procedure. In 1957 we[9] reported poor results in only 5 percent of our patients followed 18 months to seven years. Subsequently, with a longer average follow-up, the failure rate approximated 10 percent.[11] In an attempt to understand the cause of our surgical failures, and also to elucidate the difference between our rather good results and the poor results of operation described by sclerotherapists, we collected the records of 101 patients who seemed to represent surgical failures. The latter classification was based on the presence of one of

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two criteria: (1) persistence or recurrence of complications of venous stasis, such as varicose ulcer, stasis eczema, or progressive fibrosis of the subcutaneous tissues; (2) persistence or recurrence of large varices or of dilated segments of either the long or short saphenous vein.

The cause of the poor result was demonstrated in most cases by reoperation, but in a few cases only by careful clinical examination because reoperation was refused by the patient. Phlebography was frequently used when the preoperative clinical examination did not seem sufficiently accurate.

The original operation had been performed by us in 25 cases, by some other surgeon in 76.

Results

With two exceptions, all the poor results were attributable to one or more of seven causes. In several cases, reoperation demonstrated more than one cause for the failure of the first operation. Two patients had unsatisfactory result for which no cause could be detected. The proven sources of failure were as follows:

1. The long saphenous vein had not been interrupted at all and was still present as an intact incompetent trunk in 23 patients. In all of these cases the operation had been done by other surgeons, of whom at least four were board-certified in general surgery.

2. A substantial segment of the proximal long saphenous trunk was left at the saphenofemoral junction along with one or more major incompetent tributaries of the saphenous vein. In many of these patients, the situation was present bilaterally. This finding occurred in 33 patients, all of whom were originally operated upon by other surgeons.

3. A persistent length of patent dilated long saphenous vein was present in the thigh or upper calf of 11 patients, in whom the long saphenous trunk had presumably been completely removed by stripping. In one of these cases the first operation had been done by us, and in ten cases by other surgeons.

4. An intact incompetent short saphenous trunk was presented in 34 patients. This vein had not been approached at previous operation in any instance. Eight had been our patients for the original operation; the other 26 had been operated upon elsewhere.

5. Ten patients who had had short saphenous stripping still showed a significant proximal segment of that vein along with incompetent tributaries. Our group made this error in two of the ten cases.

6. The commonest finding among the surgical failures was the presence of one or more incompetent perforating or communicating veins. While this situation was demonstrated in 53 patients (of whom 10 had been originally operated upon by us), in only 13 cases was the presence of incompetent perforating or communicating veins the sole cause of poor result. In nine of these cases (operations all done by other surgeons) an adequate vein stripping had been performed but no attempt had been made to locate and interrupt any of the incompetent perforating veins. The other four patients had been originally operated upon by us, and in each case an attempt had been made to find all the incompetent perforating and communicating veins.

7. Seventeen patients, all women, had persistent large symptomatic varices because of the presence of a syndrome first described in 1966[10]—lower extremity varicosis originating from the pelvis. Six of these women had been treated by vein stripping performed by us before our recognition of this syndrome; the other 11 had been operated upon elsewhere.

The findings enumerated previously are summarized in Table 1. Obviously, the total of causes for surgical failure is greater than the total num-

TABLE 1.—*Attribution of Poor Results—Seven Causes*

	Primary Operation Done by		
	Authors	*Other Surgeons*	*Total*
Persistent long saphenous trunk	0	23	23
Persistent proximal long saphenous remnant	0	33	33
Persistent mid-saphenous remnant	1	10	11
Short saphenous not previously removed	8	26	34
Persistent proximal short saphenous remnant	2	8	10
Incompetent perforators or communicators*	4	9	13
Varices of lower extremity originating from the pelvis	6	11	17
Surgical failure for no apparent reason	2	0	2

*Only significant findings.

ber of patients because, in the majority of cases, there was more than one reason for the poor result.

Discussion

The causes for failure of varicose vein operations fall into three categories: technical errors, errors of judgment, and unavoidable failures due probably to the underlying congenital factors in varicosis.

Technical errors comprise persistence of an intact long saphenous trunk, persistence of a proximal long saphenous remnant, persistence of a mid-saphenous trunk, and persistence of a proximal short saphenous remnant. Most of these errors can be prevented by the proper placement of an incision of adequate length for the needed exposure and clear identification of the saphenofemoral or saphenopopliteal junction.

For the long saphenous vein, an incision at or above the inguinal crease, extending medially from the femoral pulse, provides easy access to the proximal end of the saphenous vein. With a thin patient, the incision may be as short as 5 cm and placed right in the inguinal fold. An incision up to twice this length may be required in an obese patient and it should be placed 1 cm or more above the fold of the groin. The dissection must be carried out to provide complete visualization of the femoral vein for at least a centimeter in every direction from the junction with the saphenous vein. Only by such exposure can one be certain properly to indentify the long saphenous rather than an accessory vein and also to locate and divide all the tributaries that enter the saphenofemoral junction. To be certain that the saphenous vein is removed in its entirety, the stripping of the long saphenous trunk should be performed from the ankle to the groin rather than from the groin distalward. Frequently a stripper passed down from the groin ends in an accessory vein rather than in the main saphenous trunk.

After the long saphenous vein has been removed, it should be inspected to make sure it is intact, for sometimes a considerable segment of the mid-portion of the vein may break off and remain in place. One should also be aware that the long saphenous trunk occasionally divides into two veins, then rejoins as one again. This double saphenous anomaly usually appears just above or below the knee. Inspection of the removed saphenous trunk may indicate that there was such a division and that one side remained in place. Excessive bleeding from the channel of the stripped vein is highly suggestive of the presence of a persistent segment of the mid-portion of the long saphenous trunk. An opening should be made at the source of the bleeding, which may be readily determined by digital pressure, and the remaining vein segment located and removed.

The proper placement of the incision for the junction of the short saphenous with the popliteal vein is sometimes difficult because of the great variation in the level at which the short saphenous enters the politeal. If the stripping is begun at the malleolar level, the head of the stripper sometimes seems to catch just distal to the level at which the saphenous turns inward to enter the popliteal vein. A transverse incision of 7 cm or more at this level, almost always some distance above the popliteal crease, may permit clear visualization of the saphenopopliteal junction. Otherwise, a proximal vertical extension, as described by Dodd and Cockett,[4] becomes necessary in order to be certain that no remnant of the proximal short saphenous is left. Adequate exposure of the saphenopopliteal junction is impossible with the patient supine.[5]

Errors of judgment comprise failure to diagnose short saphenous incompetence, failure to recognize and localize incompetent perforating veins, and failure to recognize the syndrome of lower extremity varicosis originating from the pelvis.

A dilated incompetent short saphenous vein is less easily recognized than a comparable long saphenous vein because the former is covered in the proximal half of its course by a fairly thick fascia. If it lies in a rather heavy leg, the fascia is not only covered by a layer of fat, but even the distal suprafascial portion of the vein may be masked by adipose tissue. Except in patients with considerable edema, an incompetent short saphenous vein and its dilated tributaries are usually conspicuous just behind and above the external malleolus. If there are stasis changes in this area, the short saphenous system is necessarily incompetent. Of course, the tourniquet test is most useful. If the varices fill within less than 30 seconds with a tourniquet about mid-thigh level but remain relatively empty with a tourniquet just above the knee, the short saphenous system is almost certainly incompetent.[7] Sometimes there is so much induration due to prolonged venous stasis in the leg that it is impossible to find the varices let alone interpret a tourniquet test. In the latter situation, phlebographic examination is necessary for proper planning of operation.[9]

Though it is now more than a quarter century since Sherman[12] first demonstrated the importance of dividing incompetent perforating and communicating veins, failure to recognize, localize and divide them is still a surprisingly common surgical error in the treatment of varicosis.[1,2] Dodd and Cockett[4] gave considerable emphasis to this problem in 1956 in their outstanding treatise.

Even if one is aware of the importance of incompetence of perforating and communicating veins, it is not easy to localize them for surgical correction. Too many surgeons equate saccular varices—so-called "blow-outs"—with the location of incompetent perforators and communicators. Actually, many of the blow-outs have no relation to incompetence of deeper veins, and are of significance only when they are associated with a palpable defect of the underlying fascia. We discussed the clinical localization of incompetent perforating and communicating veins in an earlier publication[9] and described the use of phlebography for finding these veins in the indurated tissue encountered in severe chronic venous stasis. Varicose ulcers are rarely seen in the absence of one or more incompetent perforating veins a short distance proximal to the ulcer.

As Sherman[13] and Dodd and Cockett,[4] among others, have pointed out, incompetent perforating and communicating veins must be dissected down to the fascia and ligated flush with its surface since tributaries frequently enter these veins a short distance distal to the point of fascial emergence.

Failure to recognize the syndrome of lower extremity varicosis originating from the pelvis is another factor in poor results. In the original description of this condition,[10] it was pointed out that there is often no incompetence of the long or short saphenous trunk despite the frequent presence of varices in the area drained by the short saphenous system. In such circumstances the surgical extirpation of a normal long or short saphenous trunk is futile. Some patients with the pelvic syndrome do have concomitant incompetence of the long (and rarely of the short) saphenous vein. The surgical removal of such incompetent trunks is of palliative value only and should be so recognized by the patient as well as the surgeon. Under such conditions, the persistence or recurrence of lower extremity varices from the pelvic veins can hardly be classified as a surgical failure.

In some cases, findings of the kind so often attributed to errors in surgical judgment may be unfairly charged to that cause. It is well recognized that the chief cause of primary varicosis is a congenital and probably hereditary predisposition associated with some defect of the valves of the saphenous veins. In light of the fact that eight patients on whom we had operated, presumably after careful preoperative examination, returned some years later with grossly incompetent short saphenous trunks, it seems fair to question whether the short saphenous incompetence was present originally or developed after the original operation. Removing varicose veins does not affect the congenital predisposition to develop new varices. The same reasoning applies to recurrence of varices due to incompetent perforating or communicating veins. Of the 13 patients in the present series in whom this condition seemed to be the sole cause of a poor result of operation, four had been originally operated upon by us. In each case, all the incompetent perforators and communicators had been sought and presumably divided. One may wonder if those perforators which later necessitated reoperation were missed in the original examination or developed later. However, it is noteworthy that in only nine of 53 cases in which reoperation revealed the presence of significant incompetent perforating or communicating veins had a search for these veins been carried out at the time of the previous operation. From this it may be drawn that the overwhelming majority of incompetent perforators and communicators found in patients with poor results are due to erroneous judgment rather than to congenital factors.

In this communication, no comment has been made on the rate of recurrence after pregnancy, as we have written of this matter in previous publications. In the current series, operation was withheld until the patients were reasonably certain to have no more pregnancies.

Conclusion

It is significant that in 77 of 101 failures of operations for varicose veins, the poor result was due to obvious technical errors. Since very few patients manifested more than one kind of error in the technical performance of the operation, it is clear that a majority of the failures were due to improper performance of the operation. A total of 64 failures were presumably due to errors in judgment. Many of these occurred in cases in which there were also technical errors. While it is not possible to determine exactly how many failures were unavoidable and presumably intrinsic in the nature of varicose veins and the limitations

of surgical treatment, it seems likely that, after properly performed surgical extirpation of variose veins, the number of unsatisfactory results over the course of years should approximate the 10 percent previously observed by us.[11] Surgical extirpation of varicoses should not be replaced by the injection compression regimen.

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DIAGNOSIS OF ACUTE FOOTBALL KNEE INJURIES ON THE PLAYING FIELD*

THE BEST TIME for diagnosing acute knee ligament injuries is on the field at the time of the injury. Later muscle spasm may mask significant injuries. The best surgical repairs are done in the first 48 hours. After 10 to 14 days, repair is virtually impossible. Therefore, the physician attending the game can perform a most valuable service by immediate, accurate diagnosis and obtaining appropriate orthopedic consultation.

Probably the most common injury requiring urgent treatment is that of torn medial collateral ligament, torn medial meniscus and torn anterior cruciate—the "unhappy triad of O'Donahue." Applying a valgus force to the knee will bring about marked laxity of the medial ligaments and the medial side of the knee will open like a book. No further examination is necessary, but surgical care is urgent. If pain is not too severe, evidence of cruciate ligament laxity as described below should be looked for. This test will be positive with the triad.

If there is questionable laxity of the medial ligament or question of internal knee injury, Drawer's sign should be attempted. A torn anterior cruciate ligament gives one the feeling of the tibia sliding forward in relation to the femur when the leg is pulled forward with the knee flexed at a right angle. If the posterior cruciate is torn, there is increased backward motion when the leg is pushed backward, with the knee flexed at a right angle. It takes considerable experience to determine which ligament causes the increased anterior-posterior laxity in a given injury. The significant point is to note the increased AP laxity and know that surgical treatment is probably indicated.

Isolated tears of the lateral or medial collateral ligament give a feeling of laxity when the torn ligament is stressed but not as much as when the cruciates are also torn.

A complete slip of the distal femoral epiphysis, a fairly common injury in football players up to age 17, can make an unwary examiner think the injury is of the knee ligaments. There is marked deformity about the knee. It is, in contrast to ligament injuries rather fixed and hard to move. When this injury is suspected, do not manipulate but splint them and have the patient transferred directly to the hospital for x-ray examination. Nondisplaced disruption of the distal femoral epiphysis will give a feeling of laxity sometimes with both valgus and varus stress. X-ray films with the joint in stress will reveal the site of the laxity.

If there is any question of collateral or cruciate ligament disruption, orthopedic consultation is urgent.

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Seminars in Virology

Alternate Immunoprophylactic and Biologic Techniques in the Control of Viral Respiratory Tract Disease

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EXTENSIVE STUDIES of acute respiratory infection in children have pointed out the pathogenic importance of the orthomyxoviruses (influenza viruses A and B) and the paramyxoviruses (parainfluenza virus types 1, 2 and 3 and the respiratory syncytial virus).[1-3] These viruses are the cause of 30 to 50 percent of significant lower respiratory tract infections in preschool children. When one considers the impact of acute respiratory tract infections on the overall perturbation of health in children of this age, these six viruses and the many rhinovirus serotypes constitute a tremendous challenge in this era of preventive medicine.

This paper will take up some of the compelling problems which must be solved in order to control these viral infections.

Parainfluenza Viruses

Inactivated vaccine combinations, consisting of the parainfluenza virus serotypes 1, 2 and 3 or these three viruses plus influenza viruses A and B, respiratory syncytial virus (and mycoplasma pneumoniae), have proved capable of evoking satisfactory serum antibody levels but, unfortunately, unimpressive protection against natural virus infection in the community.

The most recent clarification of this immunologic disappointment has evolved from the observations of Smith et al[4] that nasal neutralizing antibody correlates with protection against experimental reinfection with parainfluenza virus 1, but the presence of serum antibody fails to predict such immunity. In point of historical fact, Francis,[5] Fazekas de St. Groth[6,7] and Smorodintsev[8] marshalled similar evidence and conclusions in the 1940's and 1950's.

It seems clear that intranasal administration of attenuated or inactivated parainfluenza virus vaccines might evoke topical nasal antibody of the IgA class and consequent immunity. Nasal antibody does appear in high titer after natural infection. How long such antibody will persist and whether reinfection will incite an adequately rapid anamnestic response, thus curbing symptomatic reinfection, is not clear at the moment. There are some indications that nasal antibody may endure for at least a year.

It is to be hoped that attenuated strains of these parainfluenza viruses can be developed because one might predict that more satisfactory and continuous immunity will evolve from the greater

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antigenic imprinting of attenuated infection than is obtained by the inoculation of inactivated vaccine. In this vein, Chanock and his coworkers[9] have developed a temperature-selected mutant of parainfluenza virus 1 which replicates well in the cooler upper respiratory tract of the hamster but fails to multiply at 38°C and 39°C *in vitro* or in the vulnerable lower respiratory passages *in vivo*.

Respiratory Syncytial Virus

The respiratory syncytial virus (RSV), a common pathogen, can bring about sudden, dramatic illness and death. A mortality rate of 5 percent has been reported in the literature, but this figure may be excessive.

The nature of RSV infection in infants is surrounded by intriguing immunologic circumstances. The prominence of epidemic bronchiolitis in infants less than six months of age does not fit the usual concept of interim transplacental immunity. Approximately 60 to 80 percent of mothers should transfer some RSV immunity to their offspring for several months at least. Although transplacentally acquired serum antibody may be biologically ineffective (or perhaps the absence of nasal antibody is the crucial factor), recent speculation has focused on the possibility that maternally acquired antibody may in some way enhance natural infection.

Gardner et al[10] have reported exciting immunopathologic studies wherein surprisingly small amounts of RSV were detected in the lungs in fatal cases. Using immunofluorescent techniques, they detected antibody as well as virus in pulmonary tissue. Histopathologic evaluation of these cases of fatal bronchiolitis revealed ephithelial necrosis of terminal bronchioles, peribronchial lymphocytic infiltrate, abundant mucus plugs, the presence of cellular debris and fibrin within bronchiolar lumina, and enlarged alveolar spaces without concomitant exudate. The study of one fatal case of RSV pneumonia, on the other hand, disclosed abundant virus but no antibody. This case presented the usual microscopic findings of viral pneumonia—namely, mononuclear exudate in small bronchioles, alveolar ducts, alveoli, and the pulmonary interstices. Gardner and colleagues[10] have suggested that RSV bronchiolitis may represent either an acute hypersensitivity reaction (type I) due to the interaction of viral antigen and reagin (IgE) or an Arthus reaction (type III) mediated by complexes of viral antigen, antibody, and complement. Both of these immunopathologic reactions require the implicit conceptualization that bronchiolitis represents the second infectious and antigenic provocation with RSV. By contrast, interstitial pneumonia may result from the first encounter with RSV.

The role of maternal IgG antibody becomes important in the speculation concerning a type III reaction because the major incidence of bronchiolitis during the first six months of life seems incompatible with the likelihood of reinfection within so short a time. A type I reaction does not fit current epidemiologic concepts and does not give credence to maternal contribution to the immunopathologic phenomenon.

The speculation regarding a type III immunopathologic reaction remains unsettled since serum complement levels do not fall during episodes of bronchiolitis.[11] Furthermore, Ward and Bellanti[11] failed to detect complement by immunofluorescent techniques in the lungs of infants dying with bronchiolitis.

Compelling support for the pathogenic importance of some form of untoward immunologic injury has arisen from several vaccine trials with inactivated RSV.[12-15] These studies have demonstrated that children immunized parenterally with inactivated RSV vaccine, when challenged with natural RSV infection, incur far more significant illness than control children immunized in similar fashion with inactivated parainfluenza virus 1 vaccine. These studies indicate that some other prophylactic approach will be necessary with RSV.

Additional support for the concept of vaccine-provoked immunopathy has arisen from recent experiences with children who were immunized initially with inactivated measles virus. Following subsequent subcutaneous inoculation of live attenuated measles virus, about 5 percent of these children may exhibit a local Arthus reaction at the site of injection.[16,17] Using immunofluorescence, Bellanti and coworkers[18] detected measles virus antigen, immunoglobulin and complement in the blood vessel walls in these lesions. Furthermore, Fulginiti and Arthur[19] demonstrated delayed cutaneous hypersensitivity in children to whom inactivated measles virus vaccine was administered, but children who had been inoculated with live attenuated virus did not develop positive skin test responses to measles virus antigen.

High levels of nasal antibody have been observed with natural RSV infection, exceeding levels in the serum during early phases of infection.[20] With this lead in mind and the foregoing ad-

monitions to avoid parenteral immunization so unrefutable, there appears no alternative to the conclusion that some form of topical intranasal immunization is necessary. With techniques similar to that employed for parainfluenza virus type 1, temperature-sensitive (ts) mutants of RSV have been developed by Chanock et al.[21] In hamsters these strains mutiplied readily in the nasal turbinates but not in the lungs. Antibody production also occurred. Preliminary evaluation of an attenuated ts mutant in children and adults has been encouraging.[22,23] The same kind of perimeter defense might be achieved by the use of intranasal inoculation of inactivated RSV. Persistence of secretory IgA antibody and the potential for rapid local recall of antibody represent the crucial issues which will guide the selection of the proper vaccine. One would predict no danger of systemic immunologic injury with the modality of intranasal immunization, although it is conceivable that nasal hypersensitivity may occur.

Chanock and Wenner and colleagues[24,25] have reported RSV antigenic variants. If confirmed, this observation may constitute a significant problem. The other disquieting note is the recent observation by Loda et al[26] that natural RSV infection does not provide full protection against reinfection, thus dampening hopes for the predicted effectiveness of attenuated RSV vaccines.

Influenza Viruses

The current inactivated influenza vaccine contains two serotypic components, A2/Aichi/2/68 and B/Mass/3/66. In general, the influenza vaccines offer unsatisfactory 70 percent protection. Although a monovalent vaccine preparation of the Hong Kong strain of influenza virus A2 provided 86 percent protection against the prevailing homotypic influenza epidemic in a military environment in 1968, and 80 percent protection in school children in 1970, these observations seem to be unique.[27,28]

Recently, Kilbourne et al[29] have advanced techniques whereby the simultaneous admixture and incubation *in ovo* of heat-inactivated A2/Aichi/2/68 and chick embryo-adapted AO/PR/8/34 yielded rapidly a genetic recombinant antigenically similar to the current pathogenic strain but with the more optimal growth characteristics of the standard laboratory strain. The recombinant inactivated vaccine has proved effective in the prevention of natural influenza in man.[30,31]

Purification of virus particles by zonal ultracentrifugation and the use of adjuvant 65 (a water-in-peanut oil emulsion of aqueous vaccine with mannide monoleate as the emulsifier and aluminum monostearate as the stabilizer) permits a four-fold enhancement of the immunogenic effect of inactivated virus and antibody titers persist for a longer time interval.[32]

Beare and coworkers have compared the prophylactic efficacy of live intranasal virus inoculation with the intramuscular administration of formalin-killed virus.[33] The intranasal instillation of virus reduced by 85 percent the symptomatic infection of experimental homotypic challenge with influenza virus B2, while inactivated virus abrogated infection in only 55 percent of subjects. However, live vaccine virus infection itself proved unsuitably symptomatic.

The intriguing experiments of Waldman and his collaborators[34] have shed some light on the resolution of this vaccine impasse. Using an intranasal aerosol of commercial bivalent inactivated vaccine, these investigators demonstrated 79 percent protection against epidemic influenza A2 virus. At the same time, subcutaneous inoculation of the same vaccine protected only 27 percent of the study populace. While experimental infection with influenza virus evokes only serum IgG antibody, the intranasal aerosol of inactivated virus induces the elaboration of both serum IgG antibody and nasal IgA antibody. The particle size of the aerosol is important. Small particles induce serum antibody, probably as a result of their escape into the bloodstream from peripheral areas of the lungs, and large particles evoke nasal antibody because they settle out in the upper respiratory tract.[35]

Topical application of virus may also imprint the capacity for the cellular immunologic response of delayed hypersensitivity on the lymphocyte population of the respiratory tract. This is a factor of adaptive immunity in the lung about which we know little.

Rhinoviruses

The rhinoviruses are a very important group of respiratory pathogens in that they cause so many infections in adults as well as children. Gwaltney and his colleagues[36] demonstrated that adults may acquire two or more rhinovirus "colds" each year. Rhinovirus colds usually occur during the fall and spring months, while the newly described coronaviruses cause colds during the winter season.[37]

The rhinoviruses have been isolated from 20 to 80 percent of colds and simple upper respiratory tract infections. The attack rate of these viral infections within families may vary from 30 to 50 percent, and in ehildren under two years may be as high as 80 percent. It is unique to recover the same viral serotype from one person during repeated episodes of infection.[38]

The capability of rhinoviruses to produce lower respiratory tract disease remains a matter of controversy. Reilly et al[39] observed a few children with rhinovirus infection and lower respiratory tract involvement. On the other hand, Portnoy and his coworkers[40] have been unable to document rhinovirus pneumonitis. Although colds seem to endure longer in children, it is also true that adults may develop tracheitic and bronchitic as well as systemic symptoms suggesting lower respiratory tract tropism for the rhinoviruses. Some perspective as to this question may be gained from experimental infections with rhinoviruses.[41] Nasopharyngeal inocula produce coryza while small particle aerosols of virus, 0.2 to 3.0 microns, produce tracheobronchitis. With natural infection the biophysical characteristics of the aerosol, or secretions transmitted from an infected person, may dictate the type of illness in a susceptible contact.

The brief immunity to subsequent exposure to rhinovirus has not been explained by the production of humoral antibody or interferon. Consequent to the initial infection, the alteration of respiratory tract epithelium from columnar cells to reparative transitional epithelial cells may delete the type of cell which ordinarily is susceptible to potential reinfection.[42] Hence, heterotypic as well as homotypic resistance to reinfection, albeit brief, would accrue. Neutralizing antibody is of some importance, since a serum antibody titer of 8 or greater before natural or experimental rhinovirus exposure affords some protection against reinfection.[43]

The prophylatic approach to rhinovirus infection is an awesome, quantitative challenge because of the multitude of serotypes, numbering 100. If the serotype most important from an epidemiologic and pathogenic standpoint could be identified, a vaccine approach might prove feasible. The immunologic validity of a vaccine approach has been illustrated by the ability of intranasal inoculation of rhinovirus type 13 to induce nasal and serum neutralizing antibody. With subsequent homotypic viral challenge, rhinovirus infection developed in 80 percent of control subjects, whereas only 36 percent of intranasal vaccinees became infected.[44]

Interferon

Interferon is a protein of approximate molecular weight 26,000 which, in the course of natural and experimental viral infection *in vivo* or *in vitro*, is elaborated by the infected cell. Its primary effect is delivered to surrounding cells where, current theory suggests, interferon induces the synthesis of an antiviral protein. The antiviral protein in turn inhibits the translation of viral messenger ribonucleic acid and aborts the secondary surge of viral replication in the cells which cluster about the originally infected cell population. Interferon is produced in target tissues and plays some role in the control of viral infection in these tissues. Interferon also appears in the serum following many systemic viral infections and may modify the infectivity of viral particles delivered to sites peripheral to the site of original viral multiplication. However, serum interferon does not reach all tissues, most notably those of the respiratory tract.[45]

Not all viruses are vigorous interferon inducers, and interferon induction is not limited to viruses. Several species of bacteria, fungi, rickettsia, and protozoa elicit interferon synthesis. Indeed, in these diverse microbial species it is the double-stranded nucleic acid which switches on the production of interferon. It is the double-stranded replicative intermediate of infective viruses found within the host cell which induces the elaboration of interferon.[46] For similar biophysical and biostructural reasons, non-microbial agents may also induce interferon synthesis. The synthetic pyran co-polymer polyanionic maleic anhydride-divinyl ether and the double-stranded polyribonucleotide, polyriboinosinc-polyribocytidylic acid (poly I:C) are effective and exciting artificial interferon inducers. However, these two chemicals are toxic, in particular the pyran co-polymer.

Some experiments demonstrate that interferon inducers such as poly I:C when administered at the outset and following viral infection may modify these infections.[47] The majority of experiments indicate that pretreatment with interferon inducers is necessary for an antiviral effect. This is impractical. Passive therapy with species-specific interferon is also impractical, since the dose must be large and the production of great volumes of interferon is impossible at present. To prevent viral

respiratory tract infection, or to abort newly implanted infection during very early phases, an interferon inducing agent must be given before or at the immediate outset of such an infection.

As mentioned above, another obstacle to suitable control of acute viral respiratory disease with interferon is the distribution of systemic interferon to the respiratory tract. While intranasal poly I:C modifies intranasal influenza virus infection in mice, intraperitoneal or intravenous administration of poly I:C is ineffective.[48] Furthermore, man may be less susceptible to interferon induction by poly I:C than rodents.[49]

Although impractical for ordinary clinical practice unless confronted by rampant institutional epidemics of influenza, nasal drops containing interferon may modify upper respiratory tract infections, and fine aerosols of interferon will reach the lower respiratory tract.[45] Unfortunately, vigorous ciliary action may sweep interferon out of the lower respiratory tract on a blanket of mucus and nullify a therapeutic effect.

The future of interferon as a prophylactic or therapeutic antiviral agent in man is not encouraging. If certain components of acute viral respiratory disease, most important that caused by the rhinoviruses, continue to elude vaccine-induced disease control, the only hope resides with nontoxic antiviral drugs which may be administered daily, if for no other reason than to prevent infection. A drug which would terminate respiratory tract infections already well under way would be thrilling. In this context, continued treatment with interferon inducers may prove difficult because of the acquisition by the host of tolerance to interferon induction. Fortunately, this is less a problem with poly I:C as an inducer than with viruses.

So, the lung of man must be interferon-inducible. The lung must also be sensitive to the action of interferon. Then one must hope that the viruses of concern are susceptible to the disruption of translation of viral messenger RNA which is programmed in potential target cells by interferon. Most of the respiratory viruses seem to be so.

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EXTERNAL OTITIS (OTE)*

EXTERNAL OTITIS is an inflammation of the ear canal sometimes referred to as "swimmer's ear" and caused by excessive water in the ear canal, which provides good conditions for organisms to grow. The most common organism is one of the staphylococcus but can be streptococcus or fungus. The canal can become secondarily infected with pseudomonas seruginosa. Symptoms are pain, itching, swelling and fever, and the most obvious diagnostic sign is pain on any movement of the external ear.

Swimmer's ear, external otitis, can be divided into three categories.

1. External otitis with severe pain and fever. Treatment is systemic antibiotic and local therapy. Local treatment is to clean the external canal carefully then insert a cotton wick, then apply to the wick three to five drops of steroids with polymixin and acetic acid. Use these drops three times daily. After 48 hours, the wick may be removed and treatment continued simply by applying the drops three times a day. Swimming should be prohibited.

2. External otitis with severe pain but a minimal amount of swelling of the ear canal. Patients with this condition need to be treated only with four to five drops in the ear three times a day and elimination of swimming. No systemic antibiotics are required.

3. External otitis with periodic discomfort that clears on its own but is aggravated every time the patient goes into the water. For these patients, use of the ear drops at bedtime each day that they have been swimming usually will suffice. This is also a good preventive measure to use on those who have had severe otitis externa even after complete recovery. Ear plugs, lambs wool and other devices inserted in the ear have been found to be not only useless but sometimes harmful.

The best preventive procedure is to dry the ear after any period in the water.

An additional way to assure that the ear dries out is to add two drops of alcohol to the external auditory meatus. This decreases the surface tension of the remaining water and speeds evaporation. Swimmers typically develop a hypertrophic bar of tissue in the external ear canal that acts as a dam behind which water will accumulate.

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Post-Neonatal Sudden Unexplained Death in a California Community

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To gain further insight into the problem of infant sudden death, a study was undertaken to investigate a complete series of cases of infant sudden unexplained death that occurred during a seven-year period in Sacramento County. Needed information was abstracted from autopsy records, Medical Examiner's records and death certificates. The average death rate for the seven-year period was 1.7 for 1,000 live births. Average age at time of death was 2.8 months. There were no records of sudden death among infants over the age of eight months.

Higher than average death rates were observed within many of the low socioeconomic areas of Sacramento County. Also, sudden unexplained deaths appeared to occur more frequently in the winter months than in the spring, summer or fall. In over half the cases the infants had a cold, the sniffles, or other respiratory tract congestion within two weeks of the date of death, which seems to support the oft-quoted contention concerning the possibility of nasal obstruction which could initiate the fatal apnea. An additional notable finding was the very frequent occurrence of petechial hemorrhage in the thymus, heart, and lung tissues.

The unique age distribution of these deaths in combination with the high frequency of low socioeconomic groups and the frequency of minor respiratory ailment would suggest approaches that can be taken to identify infants at high risk and thus initiate effective community health programs for prevention.

ALTHOUGH THE PHENOMENON of sudden unexplained death in infancy (crib death) has been recognized for many decades and studied extensively,[1-12] its magnitude is not fully appreciated. In 1968 the incidence in California of this tragic cause of death in the post-neonatal period (28 days to one year) was 1.55 per 1,000 live births.[1]

A recent communication described certain factors that were found to be related to crib death.[1] The most consistent of these factors were age (a peak occurrence from one to four months of age), race (higher death rates for black and American Indian than for white or Oriental infants), birthweight (high rates for infants of low birthweight) and shortened gestational age. Other factors included low income-producing occupation of the father, younger age of mother and abbreviated or total lack of prenatal care. These findings were based, however, on information obtained from birth certificates in a cohort of live births during one year. To gain more insight into this tragic phenomenon, a study was undertaken to investigate a complete series of cases of infant sudden and unexplained death that had occurred during the period of 1964 to 1970 in Sacramento County, California.

Methods and Materials

California law requires that county medical examiners perform autopsy in all cases of sudden, unexpected or accidental deaths for the purpose of determining the exact cause of death. Information on all infants who die suddenly or unexpectedly in Sacramento County is routinely recorded and kept in the county coroner's office. Autopsy protocols for all cases of infant sudden deaths that had occurred during the years 1964 to 1970 were retrieved and reviewed; all pertinent data from these records were abstracted on a predesigned form. Pathological examinations in all cases included in this study had been performed by one of us (P. R.). To insure complete case ascertainment for the period under study, death certificates for all infants who died in Sacramento County during these years were retrieved from the files of the county and state health departments. The review of these death certificates included a systematic search for any indications of sudden unexplained death recorded on the death certificate either as "underlying cause of death," "contributing cause of death" or "consequence of death." Specific attention was given to such epithets as "crib death," "cot death," "cause of death unknown," and "sudden or unexplained death." A list of sudden unexpected infant deaths obtained from the search of death certificates was then matched with the records of the Sacramento County coroner's office. The main criterion used for inclusion of a case in this study was that sudden and unexpected death had occurred when the infant had been in good health or his terminal illness was judged to be so mild that possibility of a fatal outcome was not anticipated. In other words, the death had to be sudden and unexplained to qualify for inclusion in the study.

Our extensive and systematic search yielded a total of 128 such deaths which had occurred in Sacramento County during the years 1964-1970. In nine of these cases the babies were not residents of Sacramento County and therefore were not considered in some of the subsequent analysis of data. To avoid problems associated with neonatal deaths (for example, birth injury and congenital malformation), the age of infants selected for the study was limited to the post-neonatal period (28 days to one year). Information derived from the autopsy protocols and death certificates included data on age, sex, race, date, time and place of death, the general circumstances surrounding the death, and autopsy information on the gross anatomic and microscopic findings as well as results of other standard laboratory tests. To determine incidence rates, information on all live births during this seven-year period was also obtained from the files of the Sacramento County and State of California health departments. The seven-year aggregate of cases was then used as the basis for calculating rates and reporting the epidemiologic features of sudden unexplained death in Sacramento County.

Results

Epidemiology

As can be seen from the data presented in Table 1, the incidence of sudden death per 1,000 live births varied during the seven-year period under study. The 1970 death rate of 0.9 per 1,000 live births is the lowest recorded during this period while rates for 1964, 1966, and 1968 were the highest. A secular trend in the rate of sudden

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TABLE 1.—*Incidence Rates of Post-Neonatal Sudden Unexplained Death, Sacramento County, California, 1964-1970*

Calendar Year	No. of Live Births	No. of Sudden Deaths	Rate per 1,000 Live Births
1964	11,557	23	2.0
1965	10,554	13	1.2
1966	9,997	20	2.0
1967	9,857	18	1.8
1968	9,673	21	2.2
1969	9,938	15	1.5
1970	10,155	9	0.9
ALL YEARS	71,731	119	1.7

TABLE 2.—*Rates of Sudden Unexplained Deaths, According to Census Tract Areas, Sacramento County, California, 1964-1970*

Areas	No. of Births	No. of Deaths	Rate per 1,000 Live Births
Washington	3,889	9	2.3
Oak Park-Glen Elder	5,807	17	2.9
Del Paso-Robla	10,327	27	2.6
Cosumnes-Delta	1,841	2	1.1
Remainder of County	49,867	64	1.3
COUNTY AS A WHOLE	71,731	119	1.7

TABLE 3.—*Distribution of Sudden Unexplained Deaths, According to Month of Death, Sacramento County, California, 1964-1970*

Month	No. of Deaths	Percent Deaths
January	23	18.0
February	14	10.9
March	16	12.5
April	11	8.6
May	10	7.8
June	11	8.6
July	7	5.5
August	9	7.0
September	5	3.9
October	7	5.5
November	4	3.1
December	11	8.6
ALL MONTHS	128	100.0

Differences by month of the year are statistically significant: $X^2=28.19$, $p<.001$

death was not observed. The average death rate for the entire seven-year period (1.7 per 1,000 live births) is very close to the rate we had reported previously for the 1968 California live birth cohort as a whole (1.55 per 1,000 live births).[1]

The average age of infants at death for all cases in this series was 2.8 months. Almost 83 percent of all sudden deaths in this series of cases occurred before the age of six months. There were no sudden deaths between the ages of eight months and one year. Almost one-third (32.8 percent) of the sudden deaths occurred between the first and second month of age and over one-half occurred before the age of three months. The proportionate distribution of deaths by age at time of death was found to be consistent with findings of other epidemiologic studies of sudden unexplained death reported for the State of California as a whole, and other areas in the United States, Canada, and Western Europe.[1-14]

As has been found in other studies,[1-5,9,10] the incidence of sudden death was greater in male than in female infants (58.6 percent and 41.4 percent). However, when compared with the expected frequency based on the distribution of live births by sex, the difference in frequency of sudden death between male and female infants was not statistically significant ($p>.05$).

The rate of sudden infant death among white infants was 1.5 per 1,000 live births and among black infants it was about twice as high (3.4 per 1,000 live births). Among Oriental infants the rate of sudden death was somewhat lower than in other racial groups (1.1 per 1,000 live births).

Census tracts for Sacramento County, as defined by the U.S. Bureau of the Census, were grouped into five major areas. These areas included (1) *Washington* area (the central portion of the City of Sacramento) with 25 percent black and Mexican-American and a median annual family income of $7,500; (2) *Oak Park-Glen Elder* area with more than 30 percent black and 20 percent Mexican-American and a median family income of $6,500; (3) *Del Paso-Robla* area with 20 percent black and a median family income of $7,000; (4) *Cosumnes-Delta* area with 35 percent Mexican-American and a median family income of $9,500; and (5) the remainder of the county with a median family income of $13,500 and mostly white population. Death rates, by above census tract groups, are presented in Table 2. As can be seen, rates in the *Oak Park-Glen Elder, Del Paso-Robla,* and the *Washington* areas are noticeably in excess of the overall rate of 1.7 per 1,000 live births for the county as a whole. On the other hand, the rate in the remainder of the county is very low. The low rate found in the Cosumnes-Delta area is not significant because of small numbers ($N=2$).

Temporal Distribution

Season. The distribution of sudden unexplained deaths according to month of death for the seven-year period of study (Table 3) indicates a peak frequency during the month of January. The fre-

quency of sudden death appears to be higher throughout the winter and early spring months than it is during summer and fall. The observed difference in occurrence of sudden death according to month of the year is statistically significant ($p<.001$) when compared with the number of deaths expected on the basis of a null hypothesis of equal frequency throughout the year.

Day of the Week. The proportionate distribution of deaths by days of the week (Sunday through Saturday) showed no significant differences from the null hypothesis of equal distribution throughout the week ($p>.50$).

Time of Day. For most of the cases studied, time of death was at best only an approximation based on information obtained by the investigating coroner's deputy from the parent or guardian. Where not precisely known, time of death was estimated at the midpoint from the time the infant was last seen alive and the time found dead. The distribution of deaths by hour of death recorded on the autopsy protocol were 23.6 percent for midnight to 6 a.m., 53.1 percent for 6 a.m. to noon, 14.9 percent for noon to 6 p.m.; and 8.6 percent for 6 p.m. to midnight. This distribution by time of the day is significantly different from a null hypothesis of equal frequencies in six-hour intervals throughout the day ($p<.001$).

Marital Status of the Parents

Almost one-third (32.8 percent) of all deaths occurred in families in which either the parents were not the natural parents of the infant or where one parent was separated, divorced, or otherwise not living with the other. There are no available data for comparison to determine the significance of this observation.

Medical History

More than half of all the infants (56.3 percent) were reported to have had either a cold, sniffles, respiratory congestion or some form of respiratory ailment within two weeks of the date of death. Two were recorded to have an episode of asthma, diarrhea, and elevated temperature within two weeks before death. At the time of the autopsy no attempt was made to isolate or identify microorganisms.

Sixty-four percent of the infants were reported to have had an episode of sickness or illness some time before the date of death. These were mostly mild colds or sniffles. Over three-fourths (78.9 percent) of the infants had been seen by a physician at least once since birth. These visits were for purposes of check-ups or in conjunction with a minor illness. Fourteen infants had been in hospital at some time since birth for specific illnesses; the diagnoses included asthma, diarrhea, and anemia.

Sleeping Conditions

In 51.6 percent of cases the infants were found dead in the crib, 8.6 percent were reported to have died in bed, and 4.7 percent on a sofa or couch. For about 20 percent of all cases, the location was some other place such as a mattress on the floor. The type of room in which the infant was found dead was not routinely recorded on the autopsy protocol. Also, for 50 percent of all cases the position of the infant when found dead was not reported; but among those in whom this information was available, one half were found dead lying on their stomachs.

Pathology

Gross Findings

Most of the infants examined appeared to be reasonably well nourished. A few had a diaper rash and one infant was noted to have a minor bruise on his body. There was no evidence to suggest neglect or ill treatment in any of the cases. A frothy blood-tinged fluid was observed at the nose or mouth in 36.7 percent of all the bodies examined.

Thymus. The thymus was frequently found to be large, perhaps a normal finding for early infancy. Petechial hemorrhages were observed in 30.3 percent of all infants.

Heart. In all instances the heart was normal, with no pathological finding except epicardial petechiae, which were observed in 46.7 percent of all cases studied.

Lungs. Petechial hemorrhages or minimal edema or both were noted in all but 8.6 percent of the cases.

Brain. Minimal petechial hemorrhages scattered throughout the surface of the brain tissue were noted in 5 percent of cases.

Other organs. No gross anatomic or pathologic lesions were found in the liver, spleen, kidney, or digestive tract.

Microscopic Findings

Thymus. The tissues of the thymus were seen to be essentially normal in 54.4 percent of cases. Petechial hemorrhages alone or in combination

with hyperemia were the major abnormal findings in 42.2 percent.

Heart. The tissues of the heart were essentially normal in 54.4 percent of cases. The single most frequent abnormality was petechial hemorrhage (12.7 percent).

Lungs. Detectible edema of the lungs was noted in 77.7 percent of cases. Focal atelectasis was found in over one-half of the cases.

Brain. The most frequent abnormal finding of the brain was petechial hemorrhage, seen in 26.5 percent.

Other Tissues. The most frequent remarkable finding for other organs examined was petechial hemorrhage. The proportion of infants with these lesions in the various other organs examined were: spleen, 22.2 percent; kidney, 12.2 percent. Inflammation of the trachea or larynx was noted in 19.6 percent. All other organ systems were essentially unremarkable.

Routine laboratory examination of the blood for barbiturates, blood alcohol or carbon monoxide yielded negative results in all cases examined.

Discussion

The findings of this study confirm, in general, those of other studies conducted in large metropolitan areas[3-4] and the State of California as a whole.[1] The seven-year average death rate in Sacramento County, however, was lower than that reported in most other studies,[2-4,6,9] except Minnesota[5] and California.[1] The age distribution of infants at the time of death was similar to that in almost all other studies. Our finding of a high rate of infant sudden death among black infants confirms similar findings reported elsewhere.[2-4] That almost one-third of all deaths occurred within families where only one of the natural parents was living in the house might be interpreted to suggest the possibility of psycho-social stress manifested in single-parent families as a risk factor.

That 56 percent of the infants in this series were determined to have had a recent episode of a cold or some form of respiratory ailment appears to suggest the possibility that nasal obstruction due to a mild infection could initiate fatal apnea, as Shaw[13] suggested. Although on gross inspection there was no indication of gross obstruction of the trachea, larynx or nasal atria in any of the infants examined, microscopic studies showed that 42.2 percent of these babies had evidence of tissue inflammation of these organs.

A notable finding in this study was the very frequent occurrence of petechial hemorrhage in the thymus, heart and lungs. Petechiae are reported as an almost distinctive feature of sudden unexplained death,[14-17] but it should be emphasized that in 9 percent of our cases no such petechial hemorrhage was noted at autopsy.

Finally, it should be borne in mind that although etiologically this condition is poorly understood, it is possible to design community preventive programs aimed at identifying infants who might be at high risk and thus initiate effective community health programs to prevent this tragedy.

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Refer to: Ocular complications of rheumatic diseases—Medical Staff Conference, University of California, San Francisco. Calif Med 118:17-22, May 1973

Medical Staff Conference

Ocular Complications of Rheumatic Diseases

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* *It is important for the internist to recognize the local manifestations of systemic illnesses. This may allow for earlier diagnosis and therefore choice of appropriate therapy. At times the local complications may be of great importance in the patient's disability. Finally, an understanding of the pathogenesis of such complications may help to elucidate the pathogenesis of the associated disease. The eye is an accessible organ which not infrequently reflects systemic illness. Today Dr. Wallace V. Epstein will describe for us some of the ocular complications which may occur in the course of rheumatic diseases.*

DR. EPSTEIN:* Almost without exception patients with chronic inflammatory intraocular disease are subjected to general health examinations in an effort to find some systemic illness which might help explain the chronic inflammation within the eye. If one reads a great many of the letters of

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine

*Wallace V. Epstein, MD, FACP, Associate Professor of Medicine and consultant to the Francis I. Proctor Foundation for Research in Ophthalmology

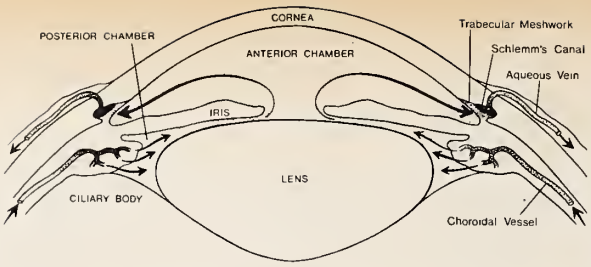


Figure 1.—Cross-section of anterior segment of eye, showing aqueous circulation from synthesis in ciliary body to outflow through canal system of the anterior chamber angle.

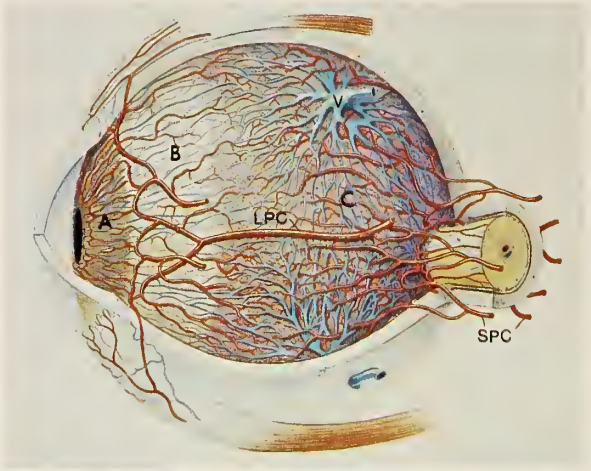


Figure 2.—Vascular circulation of the uveal tract to the choroid, (C) ciliary body (B) and iris (A). Anastomosis of long (LPC) and short (SPC) ciliary vessels is shown. Vortex vein (V) is also shown.



Figure 3.—Slit-lamp appearance of keratitic precipitates on corneal endothelium (on concave edge of center arc). Anterior chamber (dark area) separates corneal reflex from illuminated iris and lens.



Figure 4.—Nodular episcleritis of rheumatoid arthritis illustrating intense hyperemia of episcleral vessels.

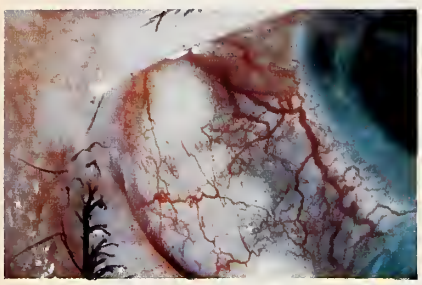


Figure 5.—Multiple scleral nodules in a patient with peripheral rheumatoid arthritis. Scleral thinning and hyperemic scleritis are also shown.



Figure 6.—Advanced scleromalacia in same patient as in Figure 5, showing blue choroid pigment and vasculature through thinned sclera.

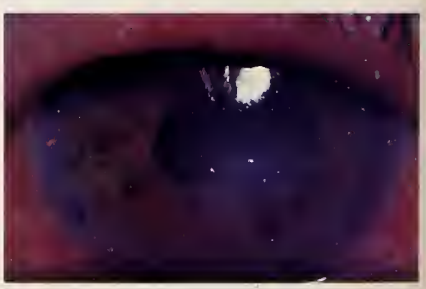


Figure 7.—Keratoconjunctivitis sicca in a patient with Sjögren's syndrome, showing filamentous keratitis manifest by irregularity and fragmentation of corneal light reflex. Note corneal filaments and edematous clouding of the cornea.



Figure 8.—Synechiae formation (irregularity of pupil margin) and cataract formation (white pupil) in a patient with juvenile rheumatoid arthritis.



Figure 9.—Band keratopathy showing calcium disposition in the subepithelial layer of the cornea in a patient with juvenile rheumatoid arthritis. Note characteristic "Swiss cheese" appearance.



Figure 10.—Acute nongranulomatous anterior uveitis in a patient with ankylosing spondylitis. Note perilimbal ciliary flush and hyperemia of episcleral vessels.



Figure 11.—Posterior subcapsular cataract in a patient with ankylosing spondylitis whose iridocyclitis was treated with topical adrenocorticosteroids.



Figure 12.—Acute conjunctivitis and perilimbal vessel engorgement in a patient with Reiter's syndrome.



Figure 13.—Keratodermia blennorrhagica in a patient with acute Reiter's syndrome.

Cost of color illustrations underwritten through the courtesy of Barnes-Hind Pharmaceuticals, Inc., Sunnyvale, California.

consultation to the referring ophthalmologist, it becomes clear that the patient might be better served if the questions raised by the ophthalmologist were more limited and if the general health work-up and diagnostic search performed by the internist were more directed toward specific related etiologic conditions associated with the various forms of intraocular disease. The frequent association of acute and chronic intraocular inflammation with the rheumatic diseases furnishes the basis for my special interest and will provide the source for the illustrations.[1]

A very brief review of ocular anatomy[2] reminds us that the term *anterior segment disease* refers to disease involving portions of the eye including and anterior to the ciliary body while *posterior segment* disease refers to disorders located in the part of the eye posterior to the ciliary body. The iris itself divides the anterior segment into an anterior and posterior aqueous chamber. The strong association of particular etiologic factors with inflammation originating in or showing preponderance in one or another location make these anatomic boundaries important. (See Figure 1.)

The distribution and the presentation of the inflammatory process is closely correlated with the vascular pattern of the uveal tract and of the retina as well as the circulation of the aqueous. Aqueous, synthesized in the ciliary body, flows through the posterior chamber and anteriorly past the pupillary margin of the iris into the anterior chamber to reenter the vascular system by way of the canal system of the anterior chamber angle. (See Figure 2.)

Several of the inflammatory diseases to be illustrated herein are associated with obstruction to aqueous flow by inflammatory adhesions (synechiae) of the iris to the lens at the pupillary edge and by diminished aqueous outflow. Both obstruction to aqueous flow through the pupil into the anterior chamber and decreased outflow at the anterior chamber angle can lead to the development of glaucoma. Diminished aqueous synthesis due to inflammation of the ciliary body may result in hypotony. The ciliary body and the outflow canal system bear a resemblance to the functions of the synovial membrane and its several functions for the joint cavity. This similarity may provide insights into the frequent association of anterior segment eye disease and some forms of synovitis.

The vascular circulatory system of the uveal tract is a second circulation separate from the retinal circulation within the eye, and a knowledge of it helps us to understand the patterns of the various inflammatory disease states. The uveal tract itself consists of the iris, ciliary body and choroid. Its vascular supply arises, as does the central retinal artery, from the ophthalmic branch of the internal carotid artery. The uveal tract vasculature derived predominately from the long and short ciliary vessels provides a path by which anterior segment disease may extend to involve the back of the eye through the choroidal portion of the uveal circulation. The reverse process may also occur. The uveal and the retinal circulations are without mutual anastomosis of blood vessels or lymphatics, thus helping to explain choroiditis without retinitis, and vice versa. Uveitis or inflammation of the iris, ciliary body and the choroid may present clinically as diseases of the vitreous, lens, or aqueous as well as of the scleral coat of the eye which communicate with the uveal tract circulation. Iridocyclitis, as seen in juvenile rheumatoid arthritis and in adult ankylosing spondylitis, follows the continuity of the uveal circulation in the sequential appearance of iritis, cyclitis and, rarely, choroiditis. Corneal disease also follows anatomic planes, with the keratitis of juvenile rheumatoid arthritis and the keratoconjunctivitis of the sicca-Sjögren's syndrome appearing in the sub-epithelial and epithelial layer, while the keratopathy of syphilis begins deep in the cornea close to the corneal endothelium. Unfortunately, adequate examination of the cornea and the anterior chamber is not possible with the ophthalmoscope alone. The corneal and anterior chamber structures on slit lamp examination may reveal keratitic precipitates on the corneal endothelium and cells and protein (flare) in the anterior chamber (Figure 3.) All of these would probably be missed if examination were done by ophthalmoscope alone. The corneal and anterior chamber disease of juvenile rheumatoid arthritis demands regular slit-lamp examination, as does the iridocyclitis of ankylosing spondylitis.

A predominately anterior chamber uveitis (Table 1) tends to be associated with diseases such as ankylosing spondylitis and the iridocyclitis associated with juvenile rheumatoid arthritis,[3] while predominately posterior uveal tract inflammation[4] should suggest toxocariasis, histoplasmosis, toxoplasmosis, sarcoidosis or syphilis. In addition to the diagnostic significance of the primary site of the inflammation, the distinction between granulomatous and nongranulomatous inflamma-

TABLE 1.—*Types of Uveitis According to Site of Predominant Inflammatory Disease*

Anterior Segment
- (a) Juvenile rheumatoid arthritis
- (b) Ankylosing spondylitis
- (c) Sarcoid
- (d) H. zoster
- (e) Syphilis

Posterior Segment
- (a) Toxoplasmosis
- (b) Syphilis
- (c) Sarcoidosis
- (d) Toxocariasis
- (e) Histoplasmosis

Both Segments
- (a) Tuberculosis
- (b) Sarcoidosis
- (c) Toxoplasmosis

TABLE 2.—*Changes in Incidence of Presumptive Etiologic Factors in Granulomatous Uveitis During the Period 1941 to 1967**

	1941 *percent*	1944 *percent*	1953 *percent*	1965 *percent*	1967 *percent*
Tuberculosis	79	52	23	4	1
Syphilis	16	17	7	0	1
Toxoplasmosis ...	0	0	26	27	18
Histoplasmosis ...	0	0	0	22	22
Undetermined ...	0	6	18	39	26

*Modified from Schlaegel, T. F., Jr.,[8] p 27.

tion is important. Granulomatous disease is characterized by posterior or anterior chamber accumulations of macrophages that clear slowly. Nongranulomatous disease is associated with polymorphonuclear cells and lymphocytes in the anterior chamber and may clear rapidly with treatment. The iridocyclitis of ankylosing spondylitis typically has nongranulomatous cell accumulations in the anterior chamber while the cell accumulations of sarcoidosis and toxoplasmosis are typically called granulomatous. It has been my observation that what may be called nongranulomatous disease at one time may be called granulomatous at another stage; however, even such inconstant hints should be grasped by the consulting physician. Granulomatous diseases tend to involve the entire uveal tract while nongranulomatous diseases tend to be limited to the anterior segment, to be acute in onset, and to be painful because of involvement of the ciliary body. The nongranulomatous iridocyclitis associated with juvenile rheumatoid arthritis is an exception in that it is frequently progressive yet painless.

The eye diseases associated with adult peripheral rheumatoid arthritis range from episcleritis or scleritis[5] to nodule formation with resultant scleromalacia.[6] This disorder is generally limited to rheumatoid arthritics with high levels of serum rheumatoid factor and usually is associated with subcutaneous rheumatoid nodules. Rheumatoid scleronodular disease illustrates the spread of the inflammatory process from the coats of the eye to the anterior chamber where a protein flare and cells are seen on slit-lamp examination. At times the posterior segment also may be involved in a retinal detachment. Figure 4 shows an example of rheumatoid nodular episcleritis in a patient who had not had active synovitis for several years. This is a not uncommon observation concerning many of the extra-articular manifestations of rheumatoid arthritis. Figure 5 shows scleritis and multiple scleral rheumatoid nodules and illustrates the perilimbal inflammation of scleritis. Episcleritis and conjunctivitis tend to be more superficial and not localized to the perilimbal area. The extension of the rheumatoid nodule within the scleral coat results, at times, in significant anterior and posterior segment disease by virtue of its anatomic proximity to these other areas. The end stage of rheumatoid nodular scleritis results in scleral thinning and exposure of the choroid, and eventually may cause scleromalacia perforans. (Figure 6)

In the keratoconjunctivitis sicca related to Sjögren's syndrome[7] we are able to see several manifestations of keratitis detectable by changes in the surface corneal light reflex. (Figure 7) The light reflex is irregular and fragmented, with clear disturbances of the epithelial layer. Patients with keratoconjunctivitis sicca show conjunctivitis and superficial keratitis; and, with further fragmentation and loosening of the epithelial layer, filaments are formed and the picture of filamentous keratopathy is seen. An unusual but tragic final consequence of this process may be corneal ulceration and perforation.

When we turn from nongranulomatous forms of ocular inflammation closely related to systemic diseases such as rheumatoid arthritis or ankylosing spondylitis to granulomatous uveal tract inflammation, we find a vast array of changing associations. The pattern of presumptive diagnoses of granulomatous uveitis has changed over the years, as is shown in Table 2.[8] It is interesting to note that in 1941 tuberculosis was thought responsible for 79 percent of cases of granulomatous uveitis and none were of undetermined cause, while in 1967 the undetermined cause group rose to 26 percent, and tuberculosis was thought responsible for only 1 percent.

The onset of anterior nongranulomatous uveitis in a child must immediately raise the question of juvenile rheumatoid arthritis (JRA). Characteristically the child has little overt inflammation or pain, and the uveitis may first be detected by the mother as variation in the pupil color (cataract), pupil irregularity due to binding of the iris margin to the anterior surface of the lens—synechiae—(Figure 8) or visual disturbance. At times the uveitis may precede the onset of overt synovitis or systemic manifestations of JRA such as fever or the characteristic rash. A complication of the uveitis of JRA, but not limited to this childhood uveitis, is the formation of a corneal band developing just beneath the corneal epithelium. (Figure 9) The calcium salt deposition may lead to vision loss when it develops in the visual axis and may be cleared by chelation after removing the superficial epithelium. A recent report by Schaller and coworkers[10] suggests an immunologic process as part of the uveitis of JRA. She reported that serum IgG antinuclear antibody is found in 88 percent of juvenile rheumatoid arthritics with chronic iridocyclitis and in only 29 percent of JRA patients without uveitis. The possibility is raised that it may be possible to predict the emergence of the ocular complication of JRA. Despite meticulous care, this eye disease of the juvenile arthritic has a grave outlook: 40 of 61 patients reported upon by Schaller and coworkers had major vision loss, blindness developing in 18 patients and secondary glaucoma in 15.[11]

In adults, anterior nongranulomatous uveitis, especially in men, frequently is associated with ankylosing spondylitis. It is remarkable that of the diseases commonly damaging the sacro-iliac joints (Table 3) all but osteoarthritis and osteitis condensans ilii have an associated ocular complication. Unlike patients with juvenile rheumatoid arthritis with anterior uveitis, adults with anterior nongranulomatous uveitis usually present with a red, painful eye. Figure 10 illustrates typical episcleritis of ankylosing spondylitis. Slit-lamp examination reveals significant anterior uveitis with spill-over of inflammatory cells into the anterior vitreous.

Recurrences of this uveitis associated with spondylitis may result in cellular deposits on the endothelial surface of the cornea (keratitic precipitates) and at the iris margin (Koeppe nodules), leading to synechiae with obstruction to aqueous flow and to the potential for developing glaucoma. Both the inflammatory process and a side effect of corticosteroid therapy may contribute to the formation of posterior subcapsular cataracts. (Figure 11) Management of these serious complications demands close cooperation between ophthalmologist and internist. It is of interest that ophthalmology has it own method of diagnosing spondylitis in that Verhoeff's test for spondylitis[8] is declared positive when the patient is unable to extend the cervical vertebrae well enough to put his chin on the chin-rest of the slit-lamp apparatus.

TABLE 3.—*Conditions Leading to Sacro-Iliitis*

1. Ulcerative colitis	5. Psoriasis
2. Reiter's disease	6. Whipple's disease
3. Ankylosing spondylitis	7. Osteoarthritis
4. Regional enteritis	8. Osteitis condensans ilii

The ocular complications of Reiter's syndrome may precede or may follow the genital and arthritic manifestations of this disorder.[13] Conjunctivitis occurs in about one-third of cases and may precede or present simultaneously with iritis, as illustrated in Figure 12. Also shown is an example of the keratodermia blennorrhagica found in about 10 percent of cases of the Reiter's syndrome. (Figure 13)

Diagnosis of the rheumatic diseases that present with or may precede ocular disorders depends, for the most part, on clinical rather than laboratory criteria. Except for the regular association of high levels of serum rheumatoid factor with the sclerononodular disease of rheumatoid arthritis,[14] there are no serological procedures that reflect directly on the process of inflammation involvement. The association of serum antinuclear antibody with the uveitis of JRA and the association of high serum levels of antibody to double stranded ribonucleic acid in some adult patients[15] with idiopathic uveitis may provide insights into etiologic and pathogenetic processes in these disorders. Other studies have indicated that immunologic reactions of the delayed hypersensitivity type directed toward uveal tract antigens are operative in several forms of uveitis including sympathetic ophthalmia.[16] The search continues for laboratory procedures which will reflect directly on the level of the intraocular inflammatory process in order to allow better-informed regulation of drug therapy.[17]

Although unquestionably desirable, effective management of the associated rheumatic disorder fails to insure an equally satisfactory response of the ocular inflammation. Both JRA and ankylosing spondylitis show poor correlation of the degree of

joint inflammation with ocular inflammation. The identification of infectious processes, especially those associated with posterior granulomatous uveitis, offers the greatest opportunity for definitive therapy. The special association of uveitis with several of the rheumatic diseases continues to offer a provocative challenge for future research.

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Acknowledgments

Figure 2 was reproduced with the permission of M. J. Hogan, MD, et al and W. B. Saunders Publishing Company from the text-book: Histology of the Human Eye (Reference 2).

Drs. M. J. Hogan and Samuel Kimura supplied the clinical eye photographs (Figures 3-12), and Ms. J. Weddell prepared Figure 1.

Refer to: Kaltreider NB: Emotional patterns related to delay in decision to seek legal abortion—A pilot study. Calif Med 118:23-27, May 1973

Emotional Patterns Related to Delay in Decision to Seek Legal Abortion

A Pilot Study

NANCY B. KALTREIDER, MD, *San Francisco*

IT IS PROBABLE that the delay in the decision to seek legal abortion until the second trimester is related to a complex of psychological and sociocultural factors. The increase in medical complications and emotional stress imposed by late abortion indicates a need for special study of second trimester applicants. Previous studies[1-4] have tended to deal with the question of the emotional impact of abortion with little attention to gestational age as a variable. This communication is based on a comparative psychological study of 18 women of similar backgrounds who sought abortion at differing stages of pregnancy.

The question of psychological issues involved with the timing of the decision to seek abortion has not been examined. In comparison with the simple procedure of terminating a first trimester pregnancy, a mid-trimester abortion by amniocentesis may involve several days in hospital, a labor of three to eight hours and the delivery of a recognizably human fetus. It is reasonable to suggest an increase in psychological stress in the latter procedure. Physicians and nurses, both educated to preserve life, report uneasiness and guilt about their role. Perhaps this discomfort is reflected in the gynecological literature, which contains considerable technical comment but is generally silent on the psychological issues in late abortions.

In a recent study, Wolff[5] noted that the data on therapeutic abortions seemed distinctly different from the recorded handling of control patients receiving curettages or vaginal hysterectomy. He comments that despite rationalizations, the uneasiness about the operation is related to concern with the issue of causing a death. Since second trimester abortion seems to pose special problems for both the patient and medical staff, an investigation of the psychological factors involved in the delay of the decision to seek abortion was planned.

In contrast to the lack of attention to emotional issues in the delay of abortion, the companion sociocultural factors have been carefully studied by Bracken and Swigart.[6] In their summary, they said: "Late pregnancy abortions, with their attendant risk of more serious medical and psychological sequelae, were *not* randomly distributed among a

From the Department of Psychiatry, University of California, San Francisco.

This study was made possible through the cooperation of Planned Parenthood/World Population of San Francisco.

Submitted November 16, 1972.

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TABLE 1.—*Distribution of 18 Women in Study as to Time They Sought Advice on Abortion*

	Early Group 1st Trimester				*Late Group 2nd Trimester*								
Week's gestation at application time	7	8	9	10	11	12	13	14	15	16	17	18	19
Number of Women	2	4	2	2	1	0	2	0	1	2	0	1	1

population of 443 women who successfully applied for an induced abortion. Women beyond their tenth week of pregnancy were significantly more likely to be under 21 years old, single, have 0 or 1 living children, be black, have not completed high school, be Protestant, have been referred through clinic or university services, and to have not used a contraceptive at time of conception." These observers share the impression that preoccupation with psychiatric criteria for abortions has tended to overshadow the actual decision-making process.

This report describes the results of detailed psychiatric interviews with 18 women of similar backgrounds who differed in the time they sought abortion. The purpose of the study was to find some clues to the intrapsychic variables which appear to influence delay in seeking abortion until the second trimester of pregnancy.

Method

The group was selected from women seen at Planned Parenthood of San Francisco in the spring and summer of 1971 with unwanted, confirmed pregnancy. Since the study was to be small and descriptive in nature, an effort was made to limit compounding factors by choosing a relatively homogeneous sample of women who were Caucasian, currently unmarried, local residents and aged 20 to 26. Eighteen out of 20 women so referred arrived for interview (Table 1). The two women who did not appear had no further agency contact and the outcome in their cases is unknown.

Following separate listing of identifying data, a structured interview of from 60 to 80 minutes was tape-recorded. An outline was employed but the material was covered in an order that seemed clinically appropriate. There was a second less structured contact with 17 of the 18 women within a few days after the abortion. The recorded material was transcribed and then evaluated with reference to a number of criteria, as illustrated in Table 2. Each of the interviews was scored (by the author) on each of the listed criteria using a scale of 1 = positive, 2 = mixed, 3 = negative. The interviews were then separated into first and second trimester groups and the score for each criterion was averaged for the group. The resulting data are depicted as a range from "very positive" to "very negative" in Table 3.

TABLE 2.—*Comparison of Average Score* on Various Criteria in Two Groups*

Group	*First Trimester*	*Second Trimester*
Number of patients	10	8
Past History		
Contraceptive usage	−	− −
Previous psychiatric problems	0	0
Significant Relationships		
Father	0	− −
Mother	0	− −
Sexual Partner	+	+
Reaction to Pregnancy		
A potential baby	−	+
Ambivalence	−	+
Denial	0	+ +
Depression	−	0
Coping Mechanisms		
Ego strengths	0	− −
Decision sharing	0	+
Post Abortion Follow-up		
Emotional reaction	+	−

*Individual numerical scores averaged and scaled
1.0-1.4 very positive (+ +)
1.5-1.8 positive (+)
1.9-2.1 mixed (0)
2.2-2.5 negative (−)
2.6-3.0 very negative (− −)

TABLE 3.—*Comparison of Various Factors in 200 Clients in a Two-Month Sample of Planned Parenthood Abortion Applicants*

	Trimester of Pregnancy		
	First	*Second*	*Unknown*
Number of clients	168 (84%)	27 (13%)	5 (3%)
Average age	21	20	
Currently single	150 (90%)	24 (89%)	
Non-white	34 (21%)	7 (26%)	
Previously pregnant	45 (26%)	9 (33%)	
Previous abortion	18 (11%)	4 (14%)	
No contraception	96 (57%)	17 (64%)	

Results

Comparison of the Study Group with the Agency Population

The 18 women who participated in the study represented a range of gestational age from seven to nineteen weeks. For the purpose of the study, the ten patients who presented at ten weeks or

less and had suction curretage were grouped together and compared with the eight patients who presented at 11 weeks or more and subsequently had amniocentesis (seven women) or continued the pregnancy (one woman).

It is probably useful to view the data on the specific group studied against the background of the total population seen for pregnancy counselling at Planned Parenthood during that period. Using January and March of 1971 as sample months, there was follow-up information available on 200 women who had legal abortions. In Table 3, a comparison of these 200 women in the general client group seen by Planned Parenthood indicates no striking demographic differences between the first and second trimester applicants. The percentage of amniocentesis patients seen by Planned Parenthood was much lower than in the Bracken and Swigar study.[6] It is of interest to note that on the follow-up forms in response to a question on feelings about abortion, 72 percent of the first trimester patients checked "positive" and only 37 percent of the mid-trimester patients so indicated.

Past History

The 18 first- and mid-trimester women in the study reported similar experiences in many aspects of their lives. Questions about contraceptive usage frequently revealed a common theme of fear of sterility leading to an almost deliberate exposure to pregnancy.

"For so long I never used anything and I never did get pregnant. I thought, 'Well, maybe I'm not able to have children'—and when I found out the pregnancy test was positive, I thought, 'At least I know I can have them.' " Both subgroups generally knew of the availability of contraceptives but used them erratically or not at all. The only "contraceptive failure" in the study was a case in which a male partner had an ineffective vasectomy. Most of the women had been sexually active for some time. Several gave a history of stopping "the pill" because of side effects or medical advice and finding no satisfactory substitute. Most of the women now planned to use a regular method of contraception post-abortion.

There seemed to be no difference between the groups in either the incidence or pattern of previous psychiatric problems. One woman in each group had had a short stay in hospital for psychiatric cause precipitated by a suicide attempt. The experience of current depression in response to the pregnancy and its anticipated loss was variable and not group-specific. A major theme in five of the 18 women (three first-trimester and two second-trimester) was the pregnancy as a fantasied replacement for an earlier loss. Two of the study patients had had an illegitimate child placed for adoption several years before the second pregnancy. One woman waited until 18 weeks to seek abortion and opened the interview by talking of her earlier experience.

"Every time I see a little girl about her size, I think about her. I think I got pregnant so that I could have a baby to make up for her. It was an accident, but it's always an accident." She presented for abortion after a prolonged period of denial: "I tried not to think about being pregnant because in the back of my mind I knew that I'd have to have an abortion."

One woman spoke of "a baby who would love me" after describing her own lack of mothering. In two instances a previously satisfying relationship with their "old man" had deteriorated and the pregnancy was initially viewed as possibly bringing back the happy times.

Significant Relationships

The relationship with both parents seemed to be more often disturbed in the late abortion group. It was most frequently characterized as a communication gap and the feeling of mutual mistrust which carried over into other adult relationships: "I grew up alone. I tried to talk to my family a lot. I guess with my German background it seemed like a sin to cry and tell somebody you're really up tight. . . . My only plan or idea now would be, well, for one thing, communicating with another person—an older person, I guess."

In contrast, members of the early abortion group often expressed a feeling of security in childhood which led them to be more comfortable handling the adult decision about abortion. The following from a woman who presented at the seventh week of gestation conveys the feeling: "My parents have always loved me and I love them and we both know it. My mother couldn't help me now and I know she'll be with me whether I tell her or not."

The relationship with the sexual partner was highly variable across the sample and ranged from engaged, stable liaisons to open promiscuity with unidentified men. The most common pattern seemed to be a brief meaningful relationship which was now terminated or existed on a day-to-day basis. In several instances, the preg-

nancy appeared to be an unsuccessful attempt to salvage a lost closeness with the partner. There was no clear difference in stability of the male tie between the early and the late groups.

Reaction to Pregnancy

The difference between the early and late abortion applicants became more clear as the actual reactions to the pregnancy were compared. In thinking about the decision-making process, it was striking that after 11 weeks there was an increasing sense of baby identity. The women who sought abortion early spoke of "this pregnancy," "my condition," or even of a "fetus"; by second trimester, it was more typical for a woman to initiate the interview with such comments as, "Should I tell you how I feel about the baby?" The one woman who had experienced fetal movement during the day preceding our interview said, "It seems like when you feel life, then you're closer to the baby, so I really haven't made up my mind yet." She wanted the doctor to tell her "what stage of the development the baby is in" and ultimately decided against abortion.

Women who presented later expressed more ambivalence about the termination of their pregnancy. Women in the first trimester occasionally felt quite negatively about the pregnancy or saw it as clear choice in their own self-interest.

"I joke about it now and then—I say, 'Oh, this kid is eating all my food up.' 'It's this kid or it's me'—it's self-defense."

More commonly in the early group a baby was seen as potentially desirable but conflicting with current life priorities. As women waited until the second trimester to seek advice, they spoke more of assessing the resources available to help them keep a child. The pregnancy seemed emotionally real to them:

"I know I can't keep the baby—it's just the idea that there's a child inside you—it's a good feeling."

"Sometimes I think I'm making another person. It would be really nice to have the baby . . . but I'd rather have it killed before it was born . . . before it has a chance to be hurt."

The mid-trimester abortion applicants uniformly described a prolonged period of denial.

"I kind of thought I was [pregnant] but I thought maybe it was a tube infection or something. I kept telling myself, 'I'm not pregnant—it's all in my mind.' I didn't want to have one so bad, I hoped it would go away."

The current denial of the existence of a pregnancy often seemed an extension of a previous pattern of flight or of frenzied activity to avoid direct coping with uncomfortable situations. The use of denial apparently shielded the women from a pre-abortion realization of loss; the standard indices of depression were low in both subgroups of the study.

All of the women involved at least one other person in the decision-making process; most often the decision was discussed with the putative father. In this emancipated group, only two of the 18 had talked with their own mothers, although many turned to the counsel of a respected older woman friend. Women in the second trimester had involved more people in the discussion and several presented for abortion after some peer pressure.

Post-Abortion Follow-Up

All of the 17 women who had abortions were contacted within a week after the experience. The reaction to the procedure was generally positive in the first trimester group, and several women spoke of it as a maturing experience.

"The feeling was relief like I had already handled the emotions. I think I gained a lot from it—a feeling of what it is to be a woman."

"I must have woken up with a smile on my face. I feel like my old personality is back to normal again."

The second trimester group had a considerably different hospital experience and often felt that they had not been adequately prepared for the discomfort of the amniocentesis. They tended to use words such as "labor," "delivery" and "childbirth" in describing the abortion. Emotions were mixed and the pattern of denial often extended to the hospitalization with much focus on the physical facilities. They spoke of "emptiness," and one woman added, "It's like having a baby but not being able to keep it." Despite their initial cooperativeness in the study, further follow-up was not possible because they were a highly mobile group who seemed anxious to close out the abortion experience.

Discussion

A descriptive study of 18 women seeking an abortion was done to delineate some of the psychological issues involved in the delay of the decision to terminate an unwanted pregnancy. The group had similar backgrounds. (The interim re-

port of the nationwide study of abortion by the Population Council[7] suggests that such patients constitute the majority of those seeking abortion.) Since age, cultural background and marital status are probably important variables in the psychological meaning of a pregnancy, it would be unwise to generalize the results to all abortion-seekers. Within these limitations, the results of this pilot study raise a number of issues.

The women who were in the second trimester group tended to have had more disturbed relationships with both parents before pregnancy, marked by little meaningful communication. One could postulate that lack of early models for sharing of a decision-making process led to frequent coping by use of denial. This rigid defense mechanism may be useful during the rapid changes of adolescence, but an unwanted pregnancy leads to eventual failure to cope by the usual methods. A look at school and social histories suggested that the second trimester group was less successful and that this poor self-image made it difficult for them to act to protect the ego from destructive forces. For women with a background of emotional deprivation, it may be particularly difficult to give up the potential love of the unborn child.

As they allowed the pregnancy to progress into the second trimester, the women became increasingly aware of an identifiable "baby." When they experienced their ambivalence in an interview setting, the emotional reality of the pregnancy was notable. The Bibring study[8] had previously noted the decidedly positive shift in cathexis with perceptible fetal movements. (When this occurred to one woman in the present study, she decided against abortion.) This factor adds to the already complex emotional problems of very late (18 to 24 weeks) abortions. In contrast to the pragmatic, rational approach of the early group, those who presented later seemed increasingly swayed by emotional factors.

After the abortion, the first-trimester group focused on a sense of relief and a desire to take up their life where they left off. The mid-trimester women generally expressed mixed feelings or tried to continue coping by denial. They described themselves as empty and having lost "a child." Perhaps the emotional cathexis of the pregnancy would necessitate a real mourning process which would only be seen in a follow-up study. The inherent problems for professional staff in dealing with these women is discussed elsewhere.[9]

This study suggests that the woman who waits until the second trimester to seek abortion may need more extensive evaluation and support. Even with open abortion laws and public endorsement, there may continue to be a group of patients unable to reach an early decision. This potentially high risk population merits further attention by the mental health professions.

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Refer to: Hawes WE, Mordaunt VL: Two years' experience with Rh hemolytic disease reporting. Calif Med 118:28-32, May 1973

Two Years' Experience with Rh Hemolytic Disease Reporting

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California law, since January 1 1970, has required that all pregnant women, regardless of outcome of delivery, be tested for Rho(D) type, that the mother and physician be notified of the result and that hospitals providing service to newborns report all cases of Rho(D) Hemolytic Disease to the State Department of Public Health. Although there has been only a gradual decrease in the number of deaths due to Rho(D) Hemolytic Disease of the Newborn since 1950, there has been a precipitous fall in the past two years. Since the commencement of reporting of the disease to the State Health Department the number of cases has also dropped dramatically. It is felt that because of our conscientiously administered reporting law the morbidity and mortality figures from HDN in California are accurate, in contrast to results obtained in most other states.

It is believed that this report reflects the first really accurate look at a large population for the incidence and mortality from Rho(D) HDN since the advent of widespread use of anti-Rho(D) gamma globulin. Review of the recent literature failed to reveal definitive data on recent incidence and mortality trends for Rho(D) HDN. A survey of state health departments also failed to produce data comparable with California's.

A number of factors have played a part in reducing the incidence and mortality from Rho(D) HDN in California—namely, required testing of pregnant women combined with the almost routine use of of anti-Rho(D) immune globulin in eligible women, early recognition and treatment of Rho(D) HDN, and the reduction in family size with an increasing percentage of primiparous mothers.

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Submitted October 24, 1972.

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SINCE JANUARY 1 1970, California law has required that all pregnant women be Rho(D) tested by an approved laboratory, and that both the woman and her physician be informed of the result. In addition, cases of suspected or diagnosed Rho(D) hemolytic disease of the newborn* (Rho(D) HDN) must be reported to the State Department of Public Health. On January 8 1971, the State Board of Public Health amended the regulations to require: (1) that the Rho(D) testing, if negative, be followed by Rho(D^u) testing; (2) that all pregnant women, regardless of the outcome of pregnancy (normal delivery, spontaneous or therapeutic abortion) be included for Rho(D) typing, and (3) that in addition to approved laboratories, such tests may be performed in an approved public health laboratory. This paper summarizes two years' experience with this program.

A survey of the recent world literature dealing with Rho(D) HDN has failed to show any reference to incidence and mortality trends due to the advent of anti-Rho(D) immune globulin. Such literature deals with the past, present, and future aspects of the disease, in either an historical approach (for example, development of exchange transfusions, pre-term delivery, amniocentesis, intrauterine transfusions, and anti-Rho(D) immune globulin) or present day treatment methods. All point up hopes that Rho(D) HDN may be eradicated through widespread use of anti-Rho(D) immune globulin, but none have attempted to document it.

Definitions

Cases and outcome of Rho(D) HDN are reported to the State Health Department of California on quarterly report forms from all maternity hospitals and hospitals licensed to receive infants under thirty days of age. The following instructions appear on the back of the reporting form:

1. *Report the following as cases:*
 a. Hemolytic Disease of the Newborn *due to Rh incompatibility.*
 b. Erythroblastosis fetalis *due to Rh incompatibility.*
 c. The only ICDA (8th revision) codes for this are *774.0* and *775.0.*
2. If the above diagnoses were not clearly made, or the only diagnoses made were Hemolytic Disease of the Newborn, or Erythroblastosis fetalis, use the following criteria:
 a. Mother must be Rh−
 b. Baby must be Rh+; or if Rh−, be D^u+.
 c. Baby must have a positive direct Coombs test (usually reported as "strongly positive").
 d. In addition, the baby may have an elevated bilirubin level.

 In such diagnoses as physiologic jaundice (Icterus Neonatorum), hyperbilirubinemia, anemia in the newborn or ABO incompatibility, *the above criteria should be applied.*
3. A diagnosis of either Hemolytic Disease of the Newborn due to Rh incompatibility or Erythroblastosis fetalis due to Rh incompatibility can occur with ABO incompatibility, and should also be reported.
4. *Do not report mothers receiving anti-Rho(D) gamma globulin (Rho GAM®) or babies with ABO incompatibility alone.*

Data Collection and Accuracy

Data have been successfully gathered from all 422 hospitals with maternity or newborn services, and the reported data are believed to be complete and accurate. Errors in reporting have been eliminated as much as possible through continuing personal communication with the persons actually filling out the reports.

In 1971 the reporting form was revised to require the person filling out the report form to designate the Rho(D) type of both mother and child. This has enabled our staff to eliminate reporting of ABO incompatibilities which had been the biggest source of error.

In order to validate deaths due to Rho(D) HDN reported to the Infant Health Unit, reported names were matched with actual death certificates filed with the Bureau of Vital Statistics in Sacramento for 1970 and 1971. Table 1 summarizes the results of this search.

The accuracy of reporting neonatal deaths due to Rho(D) HDN appears to have declined in 1971.

TABLE 1.—*Perinatal Deaths Due to Rho(D) HDN as Ascertained from Comparison of Hospital Reporting and Information on Death Certificates*

	1970	*1971*
Total number neonatal deaths ascertained ..	112	62
Number neonatal deaths reported to I.H.U.*	98	40
Number neonatal deaths recorded on death certificates	104	60
Number neonatal deaths recorded on death certificates but not reported to I.H.U. ...	14	22
Number neonatal deaths reported to I.H.U. but not recorded on death certificates ...	8	2
Fetal deaths reported to I.H.U.	67	29
Fetal deaths recorded on death certificates ..	54	27
Number fetal deaths reported to I.H.U. but not matched with death certificates	13	2

*Infant Health Unit, State Department of Public Health.

*Both *hemolytic disease of the newborn due to Rh incompatibility* and *erythroblastosis fetalis due to Rh incompatibility* are used herein so that records of the cases are less likely to be overlooked by anyone scanning the literature for reports of the disease described by these terms.

TABLE 2.—*Incidence Figures and Ratios for Hemolytic Disease of the Newborn in California (1970-1972)*

	1970				1971				1972	
	1st Q	*2nd Q*	*3rd Q*	*4th Q*	*1st Q*	*2nd Q*	*3rd Q*	*4th Q*	*1st Q*	*Totals*
Cases of Rho(D) HDN reported	355	406	392	371	316	263	243	215	219	2,780
Live births*	85,255	84,149	95,976	88,833	81,113	80,373	82,607	78,452	73,485	750,243
Cases: live births	1:240	1:207	1:245	1:240	1:262	1:315	1:341	1:367	1:336	1:270
Cases/1,000 live births	4.1	4.7	4.1	4.1	3.8	3.2	2.9	2.7	2.9	3.7
Deaths (total)	38	46	40	36	26	23	17	18	12	256
Fetal deaths	22	17	9	15	9	6	6	5	6	95
Newborn deaths	16	29	31	21	17	17	11	13	6	161

*As reported by hospitals on PKU quarterly reports.

However, the reporting of fetal deaths is more accurate. This makes for some concern about the completeness of reported cases especially in 1971 when, because of reductions in the staff, only minimal checks of hospital records could be made. There is little doubt, however, that the final number of deaths recorded is quite correct and that the number of deaths from Rho(D) HDN is approximately halved in 1971 as compared with 1970.

Results

In the winter of 1970, the Bureau of Maternal and Child Health published a summary of the first year's experience with such a program,[1] which included case reviews to determine the accuracy of reporting; the use rate of an anti-Rho(D) immune globulin; a survey of hospitals regarding availability and cost of anti-Rho(D) immune globulin; a review of a sample of reported cases of Rho(D) HDN in detail; the report of the Rho(D) HDN consultants' meeting held in July, 1970; and a table listing literature review of incidence figures. The latter table showed that the California experience in 1970 agreed with such reported incidence figures as: (1) Erythroblastosis fetalis occurs in 1 percent of all pregnancies, one-third of these are due to Rh isoimmunization (that is, 0.33 percent of all pregnancies)[2]; (2) 12 percent of marriages are with Rh incompatible people and 5 percent of these incompatible marriages result in hemolytic disease.[3]

Incidence

Review of the past nine quarters of Rho(D) HDN reporting shows that the incidence of the disease is definitely declining. The ratio of cases to live births has dropped from 1:240 to 1:336. This is well illustrated in Table 2. In looking at the number of cases per 1,000 live births, there is a drop from 4.1 in the first quarter of 1970 to 2.9 in the first quarter of 1972.

In April of 1972, a questionnaire was sent to Bureaus of Maternal and Child Health of all 50 states requesting information on the number of cases of Rh hemolytic disease occurring in each state and how these data were reported to the state health department. At the time of this report, we have received replies from 42 (82 percent) of the states. For purposes of statistical comparison the questionnaire also asked for figures on deaths from Rh hemolytic disease, total live births, fetal and neonatal deaths.

In six states cases of Rho(D) HDN are reported to the state health department. In three states data are collected from birth certificate information. Of these nine, only four states reported figures that appear to be valid when compared with the present California experience or with the incidence figures quoted in the literature. The rest of the states were not able to provide useful or comparable figures. The actual incidence ratio of cases to live births ranged in the four states from 1:644 to 1:79 (California's average incidence for nine quarters of reporting is 1:270). No state furnished figures from which the case fatality rate could be calculated.

Most of the states which responded gave us figures for their neonatal and fetal deaths. Their corresponding figures of perinatal deaths due to Rho(D) HDN seem to be grossly under-reported. For example, the number of neonatal deaths due to Rho(D) HDN divided by the total number of neonatal deaths should have been approximately 1.5 to 2 percent (based on California figures) but the 31 states' figures ranged from 0.1 to 4.0 percent (mean 1.1 percent, standard deviation 0.8 percent).

The California data indicate that Rho(D) HDN is becoming less of a problem. This can be illustrated by the decrease in infant deaths (as well as

fetal deaths) in the last 24 years. Chart 1 clearly shows the trend of deaths due to HDN as reported to the California State Bureau of Vital Statistics. In 1947 the rate of infant deaths per 1,000 live births was 0.87 as compared with 0.11 in 1971. There are several reasons for this improved situation. One reason for the decrease in both incidence and severity may be the present trend toward the limitation of family size (family planning). During the last nine years, the percentage of primiparous deliveries in California has increased from 28.7 in 1962 to 41.5 in 1970. This also tends to reduce the existing pool of Rho(D)-sensitized women of childbearing age. The disease may now be recognized early in pregnancy through typing and antibody screening of the pregnant woman's blood. The use of amniocentesis and intrauterine transfusion has enable obstetricians to keep an affected fetus in the uterus until an optimum time for delivery. Exchange transfusion as a method of treatment of the newborn affected with Rho(D) HDN has become a commonplace and safe procedure.

Since 1968, anti-Rho(D) immune globulin has

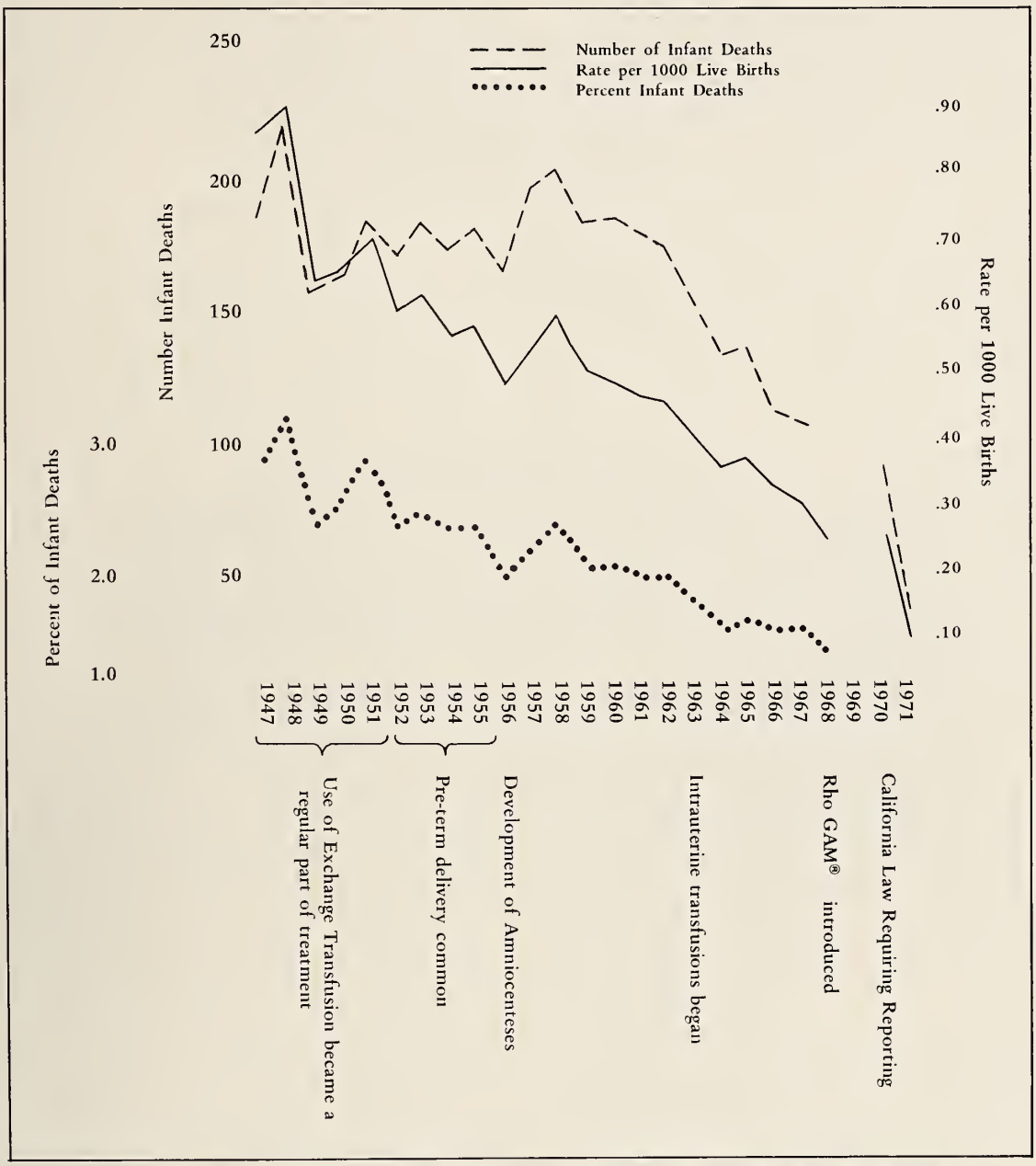


Chart 1.—Trends of infant deaths due to Rh hemolytic disease in last 24 years in California.

been available, which, when administered to an eligible postpartum woman within 72 hours of delivery of a Rho(D) or D^u incompatible fetus, will effectively block maternal sensitization to the Rho(D) antigen and thus prevent formation of anti-Rho(D) antibodies which would prove deleterious to subsequent fetuses. If the proper dosage of anti-Rho(D) immune globulin is always administered when clinically indicated, elimination of hemolytic disease due to Rho(D) incompatibility is theoretically possible. The present California regulations which require typing of all pregnant women and reporting of Rho(D) HDN have played a prominent part in encouraging the use of anti-Rho(D) immune globulin in this state. This conclusion is supported by the dramatic decline noted following implementation of this law and the other data in this report.

On the other hand California's perinatal death rate due to isoimmunization (approximately 0.45 per 1,000 deliveries) is less than half of the 1.3 per 1,000 deliveries reported in the literature[4] (Chart 1). Continued attention to prenatal testing and proper use of anti-Rho(D) immune globulin should eventually reduce the incidence to nearly zero, but progress in this regard can only be convincingly documented by careful surveillance with mandatory reporting.

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"LITTLE LEAGUE SHOULDER AND ELBOW"

COMPETITIVE ORGANIZED BASEBALL PROGRAMS for boys in the 8-15 year age group have introduced new clinical entities such as "Little League shoulder and elbow" involving the throwing arms of young pitchers.

X-ray findings are characteristic of osteochondrosis of the proximal humeral epiphysis, accelerated growth, separation and fragmentation of the medial epicondylar epiphysis, and osteochondrosis of the capitellum of the humerus and head of the radius. These result from repeated traction strains on the vulnerable un-united epiphyses of young pitchers.

Treatment is primarily preventive: Rule changes to limit the amount of throwing by pitchers should be made and youngsters must be encouraged to report elbow soreness immediately. Coaches should be discouraged from teaching adult techniques in throwing, as the conditions are often irreversible. It is urged that orthopedic consultation be obtained whenever injury is suspected.

Prepared by the Committee on Medical Aspects of Sports and Physical Fitness.

Refer to: Owens MP, Beljan JR: Congenital hypertrophic pyloric stenosis. Calif Med 118:33-37, May 1973

Congenital Hypertrophic Pyloric Stenosis

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In a large metropolitan general hospital, a high incidence of congenital hypertrophic pyloric stenosis was noted in non-Caucasian groups. Bile-free emesis was consistently reported, and admission was frequently delayed. A prompt diagnosis following admission was not always possible. Unequivocal palpation of a right upper quadrant mass was successful in less than half of the patients in this series, and radiographic studies were helpful in establishing the proper diagnosis in the remainder. Liver fracture can occur with improper abdominal palpation techniques.

Despite a surprisingly high complication rate, the ultimate result of operative therapy is uniformly excellent. Three patients not operated upon who were followed for more than two years still have evidence of gastric dysfunction. Postoperative emesis following adequate operation is not unusual, occurring approximately one-third of the time. When postoperative emesis is protracted, incomplete pyloromyotomy should be considered.

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS holds a special place in the practice of surgery because of its frequent incidence, "classical" findings, and excellent cure rate following the Ramstedt operation.[1-6]

The purpose of this paper is to review an experience with 50 consecutive cases of this entity treated during an eight-year period (1963-1970) in a large metropolitan general hospital, and to compare and contrast some of our findings with respect to the incidence, diagnosis, and complications with the findings in series reported in the literature from pediatric surgical centers.

Presented at the Annual Meeting of the American College of Surgeons, Northern California Chapter, San Francisco, May 15, 1971.

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Clinical Material

The 50 infants, 39 boys and 11 girls, whose cases are here reviewed were seen at the Sacramento Medical Center, a large metropolitan general hospital with heavy experience in trauma and acute disease. Thirty-eight of the infants were of

Caucasian background, the remainder equally divided between the Afro-American and Latin-American races. Only eight were first-born males, and four were first-born females. Ten of the infants had a sibling with the same disease entity. Three were premature, the remainder full-term.

Clinical Presentation

History. A well-defined symptom complex has uniformly been reported.[7-10] The single most consistent presenting symptom was bile-free emesis, which was present in all cases. Projectile vomiting, however, was described in only 20 infants. Constipation and failure to thrive were both presenting complaints in this group. The average duration of symptoms was about ten days, with the shortest period two days and the longest 21. The average age at onset was four and a half weeks, with the the youngest two weeks of age, and the oldest eight weeks.

Examination. Physical findings have historically been of prime importance in establishing a preoperative diagnosis.[7-10] Visible peristaltic waves passing from left to right in the upper abdomen were noted in only 17 of the 50 infants in the present series. A firm spherical tumor mass was noted on palpation of the abdomen (confirmed by at least two examiners) in 24 of the infants. An equivocal finding of a mass in the right upper quadrant, necessitating a radiological contrast study for diagnostic confirmation, occurred in 18 cases. In seven of the infants, a tumor mass was not palpable, but the diagnosis was made by subsequent upper gastrointestinal series. In one instance, the correct diagnosis was established only by postmortem examination.

The state of hydration on admission was recorded as mild, moderate, or severe, depending upon body weight, skin turgor, and urinary output. On this basis, 34 infants were described as mildly dehydrated, eight as moderately so, and an additional eight as severely dehydrated.

Laboratory Studies. The carbon dioxide content of the blood, which tends to provide prognostic information regarding an infant's ability to withstand a general anesthetic,[2,4,5,11] was recorded in all 50 cases. In 31 cases it was reported normal (24 to 28 mEq per liter), in ten moderately alkalotic (28 to 32 mEq) and in eight severely alkalotic (greater than 32 mEq). In one case the carbon dioxide content on admission was 10 mEq per liter.

The association of hyperbilirubinemia and congenital hypertrophic pyloric stenosis has been reported and discussed without a substantiated cause for this apparent relationship.[2,12,13] Six of the 50 patients presented with hyperbilirubinemia ranging from 2.1 mg to 9.7 mg per 100 ml. The bilirubin elevations in five of the six cases primarily represented the indirect-reacting fraction.

Treatment

A Ramstedt pyloromyotomy was performed in 46 of the 50 cases. General inhalation anesthesia was used in 44 cases, local infiltration anesthesia in two. Delays before operation averaged 2.4 days; the longest dalay was ten days. This time included time for diagnostic confirmation and preoperative fluid and electrolyte replacement therapy.

Four patients were treated non-operatively by a regimen utilizing intravenous fluid and electrolyte infusion, alternating nasogastric lavage and gavage, and graded feedings. There was one death in this group, that of an infant who presented with a three-week history of bile-free emesis, a carbon dioxide content of 10 mEq per liter, and severe dehydration. A diagnosis could not be established on physicial examination. Death occurred on the second hospital day despite aggressive attempts to correct the fluid and electrolyte imbalance. The remaining three patients not surgically treated required hospital stays of 12, 14, and 15 days. They have been followed for a minimum of two years, and each has intermittent symptoms of gastric dysfunction, poor feeding habits, intermittent episodes of nausea and vomiting, and retarded growth and development.

Results

The long-term results in all the 46 patients' cases were excellent, despite a postoperative complication rate of 26 percent (Table 1). There were eight complications not directly related to the intraoperative procedure, comprising seven cases of bacterial pneumonitis and one of aspiration pneu-

TABLE 1.—*Postoperative Complications in a Series of 46 Cases*

Right lower lobe pneumonitis	7
Aspiration pneumonitis	1
Wound infection	3
Incomplete pyloromyotomy	1
TOTAL	12

monitis. There were three minor wound infections. In one case, the pyloromyotomy was incomplete, and reoperation was necessitated on the third post-operative day.

Intraoperative duodenal perforation occurred in 18 instances (39 percent), but in all instances the lesion was recognized at the time of operation and the duodenal opening was suitably closed. In two instances, a fracture-hematoma of the anterior margin of the right lobe of the liver was found at laparotomy. This was probably related to the frequency of preoperative physical examinations and overenthusiasm or frustration on the part of an examiner.

Postoperative Management

Oral intake was begun four to six hours after operation unless there had been duodenal perforation. The feeding regimen was generally uniform, and consisted of increasing hourly increments of glucose solution for four to six hours. If this was well tolerated, quarter-strength to half-strength formula feedings were begun. In cases complicated by intraoperative duodenal perforation, a small nasogastric tube was connected to dependent drainage for 24 hours, and the feeding regimen was then begun following removal of the tube. There were 14 instances (30 percent) of postoperative emesis of more than one feeding.

The average postoperative hospital stay was 4.5 days.

Associated Congenital Anomalies

There were nine infants (18 percent) with associated congenital anomalies, which included bilateral inguinal hernias (3), interventricular septal defects (3), patent ductus arteriosus (1), cryptorchidism (1), and microglossia (1).

Discussion

Several pertinent points relating to the diagnosis and treatment of congenital hypertrophic pyloric stenosis need reemphasis on the basis of the cases represented by this experience. The 4:1 ratio of males to females is quite typical, but the non-Caucasian incidence of 24 percent is not.[2,7] The average age at onset of symptoms has been reported as three weeks, and the duration of symptoms before treatment as one to nine weeks.[5,6,14] In this series, the average age at onset was 4.5 weeks, and the average duration of symptoms 1.5 weeks. Bile-free emesis, a constant presenting symptom in cases reported in the literature,[2,5-10,14] was present in all cases in our series.

The need for appropriate preoperative replacement therapy to correct dehydration and electrolyte imbalance is well recognized as an important prerequisite to the attainment of satisfactory operative risk.[2,4,5,11] The fact that there were no operative deaths in this series reflects, in part, adequate intravenous replacement therapy before operation.

Hyperbilirubinemia has been reported as an occasional finding with congenital hypertrophic pyloric stenosis. No apparent causal relationship exists with this association, but the coincidence was noted in six cases in our series—a higher incidence than previously noted in the medical literature.[2,12,13]

Non-operative treatment of this condition has some proponents (primarily in the European medical community), but results are generally disappointing.[10,15-18] Four of the patients in this series were treated non-operatively. Because of extreme dehydration and acidosis, one infant died on the second hospital day, never having attained suitable operative-risk status. The remaining three required prolonged stay in hospital and detailed nursing care. All three have persistent gastric dysfunction and have failed to thrive.

Often when an infant comes to a teaching institution with a presumptive diagnosis of congenital hypertrophic pyloric stenosis, he may be examined by more than the usual number of trainees. Despite admonitions to the housestaff on the inherent dangers of vigorous digital abdominal examination in an irritable infant with a tense abdominal wall, two patients early in this series were found to have fracture hematomas of the anterior margin of the right lobe of the liver at the time of laparotomy. Since this complication has been recognized, irritable infants with tense abdomens are examined during oral feeding and concomitant nasogastric decompression.[19]

Reviewing and evaluating a series of this type occasionally leads to a challenge of preconceived ideas. It has been often stated that this disease frequently involved the first-born male in a family, but in this study the incidence of first-born males was only 16 percent. We therefore support the conclusion of Delprat and Pflueger that pyloric stenosis is not a "disease of the first-born."[20] It has also been stated that one's diagnostic acumen is deficient when an infant presents with a "classical" history for this disorder, and a right upper-



Figure 1.—Radiographic confirmation of congenital hypertrophic pyloric stenosis—"string and shoulder" sign.

quadrant abdominal mass cannot be palpated. A mass was palpated in fewer than half the cases in the present series. Fortunately, the addition of an x-ray contrast study to help confirm or exclude the diagnosis is well tolerated and easily done.[21-23] The diagnosis is confirmed radiographically by the finding of either a "string-and-shoulder sign," or a "doubletrack sign" (Figures 1 and 2). There were no false-positive diagnoses in this series.

Technical Considerations

The genesis of a curative operative procedure for this pathological entity occupies a special place in the history of surgery. Until 1907, gastroenterostomy was commonly used in the treatment of this condition, but the operation often carried a mortality rate of 50 percent or more.[8-10]

Fredet, in 1907, introduced longitudinal pyloromyotomy with transverse approximation of the pylorus.[10] In 1912, Ramstedt used longitudinal pyloromyotomy alone, and the operation which bears his name has withstood the test of time.[2,5,6,10,14]

Many types of abdominal surgical incisions have been recommended, and each has its proponents.[24] Historically, however, the various abdominal wall incisions recommended were developed in an effort to minimize wound dehiscence and evisceration, which carried a high mortality in debilitated infants who did not have the benefit of modern preoperative fluid and electrolyte replacement therapy. These recommended incisions cover the spectrum from right paramedian muscle-retracting incisions, to subcostal muscle-splitting



Figure 2.—Radiographic confirmation of congenital hypertrophic pyloric stenosis—"doubletrack" sign.

incisions, to transverse incisions with rectus transection, and finally, to transverse skin incisions with rectus retraction or rectus splitting. In the well-prepared infant, the abdominal incision essentially becomes one of cosmetic consideration only.

Right paramedian incision was used in 18 of the 46 operative cases in this series, subcostal with muscle splitting in nine, transverse with rectus transection in 11 and transverse with rectus splitting in eight. All three wound infections occurred in the latter group. In no case did dehiscence occur.

Potential morbidity and mortality secondary to the Ramstedt procedure are primarily related to an unrecognized duodenal perforation or an incomplete pyloromyotomy, although the latter complication is infrequently reported.[2,4,5,7-9,16] In no single operative procedure in the surgeon's armamentarium is the admonition "Stay out of the duodenum!" more appreciated and earlier learned than in treating one's first case of congenital hypertrophic pyloric stenosis. Despite this level of awareness, duodenal perforation occurred in 18 of the 46 operative cases in the present series. An



Figure 3.—Longitudinal section of pylorus demonstrating hypertrophied circular muscle and the duodenal "fornix."

appreciation of the anatomy of the hypertrophied pylorus and the duodenal "fornix" (arrow, Figure 3) is necessary for the correct performance of the Ramstedt procedure.

A longitudinal incision on the anterosuperior pylorus is carried several millimeters proximally and distally beyond the gross extent of the hypertrophied pylorus to allow the normal seromuscular layers at the antral and duodenal ends to "give" when the pyloric musculature is divided. The hypertrophied circular muscle is gently split throughout its length until the pyloric mucosa bulges to the level of the serosa. By gentle compression of the antrum, a leak at the duodenal end is made readily apparent. Occasionally, it will be necessary to suture-ligate a small bleeding vessel at the proximal or distal end of the pyloromyotomy.

Complications

Postoperative emesis after the initiation of oral intake generally does not imply a continued obstruction at the pylorus.[2,5,6] It may, however, reflect a hurried postoperative feeding schedule.[25] Fourteen of the 46 patients who were surgically treated had transient postoperative emesis (more than two episodes) in the early feeding period. In only one instance was postoperative emesis protracted, and in that case a subsequent gastrointestinal contrast study revealed an incomplete pyloromyotomy. Re-operation was carried out the third postoperative day without sequellae.

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MEDICAL PROGRESS

Current Transfusion Therapy

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In 1971, the American Red Cross prepared almost three million units of whole blood and approxi-480,000 units of concentrated red cells, 200,000 units of platelets, 250,000 units of fresh frozen plasma, and 180,000 units of cryoprecipitate.[1] It is estimated that this was only half of the total blood products prepared in this country, and that these products were given to almost three million patients. The steadily increasing use of blood and blood derivatives by physicians of all specialties dictates that these physicians be informed of current advances and recommendations in transfusion therapy. This communication summarizes recent developments in blood storage and component preparation and use. Further, since hepatitis represents the most common serious complication of transfusion, and because many advances have been made recently in donor screening of hepatitis, a brief discussion of post-transfusion hepatitis is included.

Blood Preparation and Storage

The cornerstone of effective, safe, and economical transfusion therapy is the proper use of blood components. Preparation of blood components has been made possible largely with the development of multicompartmentalized plastic containers which permit easy and safe separation and handling of products. Chart 1 outlines the preparation, the cost, and the major indications for these components. More detailed descriptions are available elsewhere.[2-4]

When whole blood is withdrawn from the donor it must be immediately anticoagulated and satisfactorily preserved until use. Most blood today is preserved in acid-citrate-dextrose (ACD) solution, though several potentially superior methods are available. The importance of such methods is apparent when it is considered that approximately 600,000 units of blood yearly must be discarded because of "outdating," a figure which could be reduced by 65 percent with even a seven-day extension of current ACD shelf-life.[5]

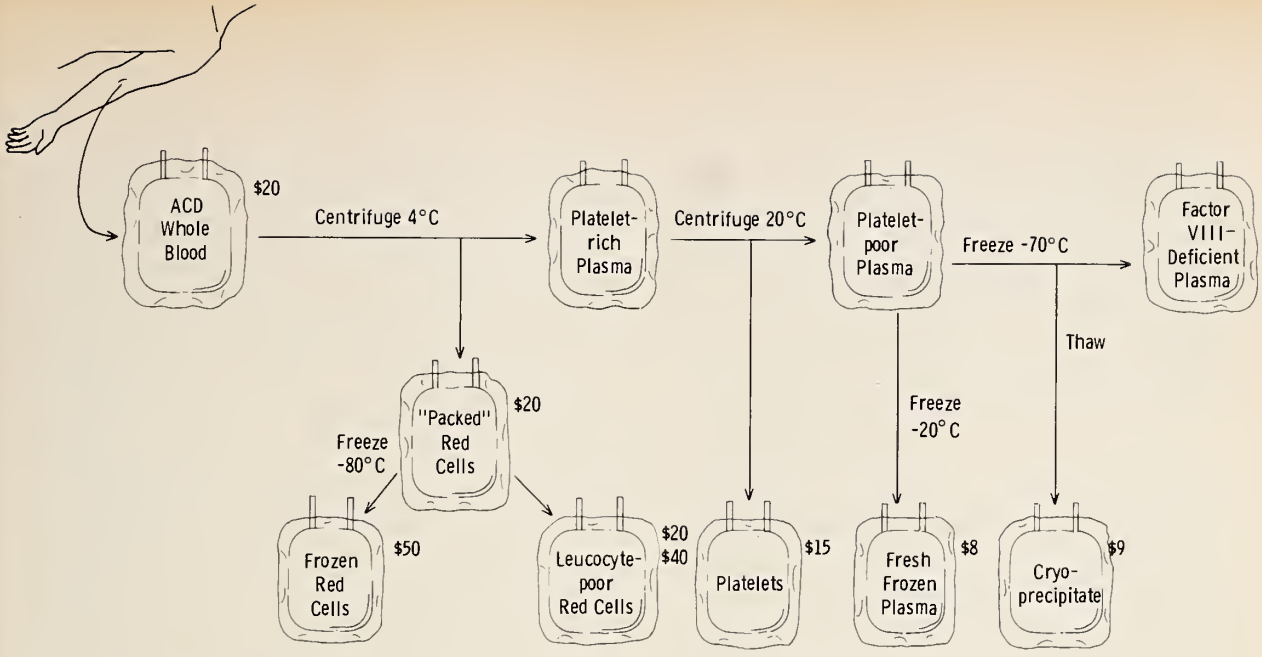
Anticoagulation

Various anticoagulants, primarily heparin, edetate disodium (EDTA) and citrate have been used in blood transfusion. Heparin, perhaps the safest additive because of the very small doses needed, has a complex mechanism of action, inhibiting multiple steps in the clotting mechanism. However, after approximately 48 hours, blood maintained in heparin may slowly clot.[6] Heparinized blood must therefore be used within 48 hours.

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PRIMARY INDICATION	Anemia and Hypo-volemia	Organ Transplant Patients	Anemia	Leucocyte Reactions	Thrombocyto-penia	Multiple Factor Deficiency	Hemophilia A	Hemophilia B

Chart 1.—Component Preparation

NOTE: Factor VIII may be prepared as concentrates from plasma by precipitation with ether or alcohol or by Cohn fractionation. Factor IX may be prepared as concentrates from plasma by Cohn fractionation and column absorption-elution techniques.

The costs shown represent charges to the patient at UCLA hospital, exclusive of crossmatching fee and laboratory fees, the sum of which add about $25 to the price of all products except platelets and cryoprecipitate. Leukocyte-poor red cells may be in the form of washed red cells or buffy coat-poor red cells, the higher price shown being for the former.

Heparin finds limited usefulness in exchange transfusions or occasionally in pump-oxygenator priming for open heart operations.

Citrate and EDTA prevent coagulation by binding calcium. Although citrate is not as effective as EDTA on a molar basis, it is used almost exclusively.[7]

Defibrinated blood, as obtained from cadavers freshly dead of sudden causes, will not clot and can be used for transfusion. Several liters of blood may be obtained from each cadaver and stored at 40°C, with only glucose added. Red cell survival is essentially normal.[8] Russian experience with this method has been extensive although only a small percentage of transfused blood is so obtained, and for technical reasons even this is decreasing.[9]

Red Cell Changes Associated with Storage

Progressively longer periods of pre-transfusion storage result in lower 24-hour post-transfusion survivals, though subsequently cells are lost at a similar rate—that is, nonviable cells are lost within the first 24 hours of transfusion. The combination of erythrocyte changes that result in this altered survival is termed the "lesion of storage."

Morphologically, stored cells become increasingly spherical, less deformable and more viscous.[10] Membrane lipid falls and critical hemolytic volume (a measure of osmotic fragility) decreases. These changes in part contribute to decreased post-transfusion survival *in vivo*.[11,12] Maintenance of a deformable disc shape is most important since the erythrocyte must pass through the microcirculation of organs such as the spleen where vessel diameter (3 microns) is small compared with erythrocyte diameter (8 microns).[10,13] Measurements *in vitro* of critical micropipette diameters for passage of unstored (disc) cells and stored (sphere) cells confirm these postulates[13] and suggest that early removal of stored cells may reflect this morphologic change. The role of adenine in reversing these changes is discussed below.

In addition to these morphologic changes, ACD-

TABLE 1.—*Alterations in Stored Blood**

Substance	Normal Donor	Days Stored in ACD 0	7	21
pH	7.4	7.0	6.8	6.6
Plasma hemoglobin-mg per 100 ml	5.0	7.0	25.0	100.0
Plasma K+-mEq/L	4.0	7.0	14.0	23.0
Plasma Na+-mEq/L	140.0	150.0	148.0	142.0
Lactic acid-mg per 100 ml	10.0	20.0	70.0	140.0
Dextrose-mg per 100 ml	100.0	330.0	280.0	220.0
Plasma ammonia-mg per 100 ml	50.0	50.0	260.0	680.0

*Modified from Huestis.[35]

stored cells show a progressive lowering of almost all erythrocyte enzymes, with a critical fall in certain phosphate compounds. Such changes are not seen in freshly frozen stored red cells, thus providing a biochemical basis for cryopreservation.[14] The relationship between these metabolic alterations in stored blood and various blood additives is discussed below.

As a consequence of these metabolic alterations, a number of toxic materials accumulate in the ACD-stored blood unit (see Table 1). The rises in extracellular potassium and acid are especially important in the multiply transfused patient, for whom therefore "fresh" whole blood or packed cells are preferred.

Two factors must be considered in evaluating the effects of storage on erythrocytes: (1) post-transfusion erythrocyte survival and (2) post-transfusion erythrocyte function. These are discussed in the following sections.

Erythrocyte Storage and Viability

In the last several years a virtually complete changeover from glass vacuum bottles to plastic bags has been achieved. The major reason for this change appears to be the relative ease, with the plastic bags, of separation of plasma, platelets, and other components for specific therapy. Other claims for the plastic bags, such as a reduced incidence of bacterial contamination, improved red cell viability, and superior platelet preservation, have been discounted,[16] although it is certainly true that the rare case of air embolism in the donor should be completely eliminated. The cost of the plastic containers, with added equipment needed for transportation and storage, probably exceeds that of the glass containers. Neither may be re-used.

ACD solutions now are used in the United States to the virtual exclusion of other red cell preservatives. Glucose, on which the red cell is almost wholly dependent for its metabolic needs, and citrate were used in early years, but the mixture yellows on autoclaving and for this reason citric acid was added to lower the pH and prevent the discoloration. Unexpectedly, red cell viability was increased, and thus the first ACD solution emerged. Today approximately 450 ml of whole blood is drawn into 67 ml of ACD solution giving a total volume of 517 ml with a resultant pH of 7.0. ("National Institutes of Health ACD-A solution"). Whole blood collected in this manner will show an immediate loss of about 5 percent of the cells ("lesion of collection"). The lost cells are apparently those at the very beginning of collection which, when coming into contact with the hypotonic acidic preservative medium, are injured and subsequently are hemolyzed. ACD-blood stored up to 21 days will show a 70 percent or better survival 24 hours after infusion. This 70 percent survival was apparently arbitrarily taken, in 1943,[2] as the minimally acceptable post-transfusion survival and therefore defines the shelf-life of ACD blood against which other methods are measured.

CPD. Citrate phosphate dextrose solution was developed in the middle 1950's to alleviate some problems inherent in ACD. Specifically, a higher pH, lower citrate content, more isotonic solution, and a longer shelf-life were desired. Early studies indicated an extension of shelf-life to about 28 days. Present studies reveal only a slight difference in survival at 21 days: 79 percent CPD against 75 percent ACD, though this difference may be more pronounced at 28 days.[17] Effects of the CPD solution on intracellular metabolism are discussed below. Despite some problems with platelet clumping,[18] CPD-preserved blood has recently been licensed for commercial use and currently is used on a limited basis in this country. It is expected that a gradual switch from ACD-preserved to CPD-preserved blood will be seen in the next few years.

ACD plus adenine. As mentioned previously, stored erythrocytes show a rapid fall in critical phosphate compounds. Attempts to maintain ATP levels have been made through the use of additives, especially adenine, which is then incorporated into ATP. Numerous studies[19-21] confirm that adenine maintains ATP levels of ACD blood for considerable periods and that even after 42 days of storage a satisfactory (greater than 70 percent) 24-hour post-transfusion survival will be obtained. Good evidence has been advanced that the adenine-induced maintenance of ATP results in preser-

vation of the erythrocyte's disc shape, preserving its deformability, hence improving its post-transfusion survival.[10] Multiple unit transfusion with ACD-adenine blood stored 28 to 42 days has been performed and shown to be without toxicity,[19] even in traumatized humans with severe acute blood loss.[21] A single report of nephrotoxic injury in non-human primates[22] needs further investigation. ACD-adenine solutions are currently in use in Sweden; it seems likely that clinical trials in this country on a larger scale will be undertaken in the future.

Erythrocyte Storage and Function

The single most important objective in red cell transfusion is maintenance of tissue oxygenation—volume depletion may be corrected with cell free fluids. Transfusion of viable but poorly functioning erythrocytes will not accomplish this objective, and in critically ill patients requiring multiple transfusions it could aggravate tissue hypoxia.[23] For this reason, considerable attention has focused on changes in hemoglobin affinity occurring in stored blood, and the relationship between these changes and 2,3-diphosphoglyceric acid (2,3-DPG), an organic ester found in red cells. Recent reviews[18,24] summarize these changes: ACD-stored blood shows a progressively increasing oxygen affinity with progressive storage time manifested by a left shifted hemoglobin-oxygen dissociation curve; 2,3-DPG has been shown to be critical in maintaining normal oxygen-hemoglobin affinity (probably through steric alterations in the hemoglobin molecule) and hence a normal oxygen dissociation curve; 2,3-DPG levels have been shown to fall at about the time of the observed left shift in the oxygen dissociation curve, dropping about 75 percent after two weeks;[25] maintenance of 2,3-DPG levels has been shown to maintain a normal oxygen dissociation curve. These changes are partially reversible after transfusion, as 2,3-DPG levels will rise to about 50 percent of normal in 8 to 24 hours. While 2,3-DPG levels are of little practical concern in small transfusions to relatively healthy patients, such considerations may be important in multiply transfused, critically ill recipients. Thus, one study of multiply transfused patients after use of standard ACD blood indicated a lowering of the oxygen P50 from 27 mm of mercury to 18 mm.[26]

The level of 2,3-DPG in stored blood may be maintained by several methods. Addition of methylene blue—which may act as a catalyst in the synthesis of 2,3-DPG—in amounts less than that used to treat methemoglobinemia will maintain 2,3-DPG levels for up to six weeks.[24] Storage of red cells in the frozen state maintains normal 2,3-DPG levels even up to several years.[23] CPD solution, apparently because of its higher pH, will preserve 2,3-DPG levels more efficiently than ACD.[27] Most commonly, however, inosine which is incorporated into 2,3-DPG, is added.[24,28,29] ACD-adenine-inosine solutions have been investigated and found to be both safe and effective in prolonging red cell viability and 2,3-DPG levels.[30,31]

Frozen Red Cells

The desire to store rare blood types for prolonged periods provided much of the initial impetus to develop methods of freezing red blood cells. At present, transfusion of frozen red cells finds several uses and is likely to increase greatly in the near future.

Freeze Injury

Freezing is a complex phenomenon which, except at absolute zero, is not an all-or-none process.[32,33] As temperature falls, tetrahedrons of water join to form ice. Between these rigid crystals of ice remains a finite volume of unfrozen water and, in living cells, solute. The result is an ever increasing solute concentration in the remaining water. At salt concentrations of 8.5M or greater, red cells become increasingly fragile and may hemolyze. The damaging effects of hypertonicity take time: at more rapid rates of freezing, damage is considerably lessened.

Freezing Methods

Human cells are regularly injured by freezing and for this reason "cryoprotective" substances are added. Red cell freezing methods may be considered in two broad categories: rapid freezing with extracellular cryoprotective agents and slow freezing with endocellular cryoprotective agents. Both methods utilize concentrated red cells in ACD solution at a hematocrit of about 80 percent.

Rapid freezing techniques,[32-34] because of the inherent relatively low grade damage to red cells, employ extracellular protective agents at low concentrations, thereby minimizing the post-thaw washing phase. Liquid nitrogen at $-196°C$ is used for freezing. A variety of extracellular protective agents have been used (dextran, hydroxyethyl starch, polyglycol, polyvinylpyrollidone or PVP), all apparently causing red cells to shrink

and extrude most of their water-solute content. The cost and bulk of the apparatus for rapid freezing techniques seem at present to be prohibitive for general use.

Slow freezing techniques[32,33,35] utilize simpler freezing equipment but require greater protection for the red cell and hence a more extensive post-thaw wash phase. These techniques are in general clinical use today. Freezing is achieved in a mechanical deep freeze at about −80°C. The protective additive is "endocellular"—so called because it equilibrates evenly across the erythrocyte membrane. The agents used (dimethylsulfoxide, ethylene glycol, glycerol) are all effective through hydrogen bonding to water, thus preventing the damaging solute exclusion seen otherwise. By far the most widely used agent to date has been glycerol, although extensive post-thaw washing to remove the glycerol must be performed to avoid hemolysis on transfusion.

Thawing and Washing Methods

The post-thaw wash method most widely used to date has been the Huggins' cytoagglomeration method.[36] After thawing, the cells are washed with a series of glucose-fructose rinses. The rinse eliminates the glycerol and, by virtue of the low ionic strength, agglomerates the red cells which then sediment and may be separated from the rinse fluid. After the rinse is separated from the agglomerated erythrocytes, the latter are resuspended in saline solution, causing dissolution of the agglomerates, and then stored at 4°C to be used within 24 hours. Apparently because of globulin attached to the red cells during the agglomeration, cells so prepared are Coombs positive, though they show no evidence of decreased survival. The sample specimen must be washed several times for crossmatching.

Another post-thaw wash method now in use is Merryman's continuous centrifugation technique.[37] The freezing and storage of the red cells are quite similar to the Huggins technique, with the important exception that the freezing medium is of significantly higher ionic strength due to the addition of saline solution. (This is not feasible in Huggins' technique since it would lessen agglomeration and recovery.) The frozen cells are thawed and diluted, then washed free of glycerol in a specially designed centrifuge and used within 24 hours. Cells prepared by this method are not Coombs positive.

To date there has been considerably more experience with the Huggins technique. It is dependable and produces an acceptable clinical product at a cost comparable to that of other freezing methods. However, the time required in preparation may be slightly greater, and the recovery definitely less than with the Merryman technique—perhaps 50 to 75 percent *in vitro* recovery as against 90 percent or more for the Merryman method.[37,38] Furthermore there is evidence that Huggins-prepared cells may not be stored in the frozen state for longer than two years, or hemolysis will result on transfusion.[38] While such figures are not yet available for Merryman-prepared cells, cells prepared in similar fashion (using relatively high ionic strength storage media and continuous centrifugation for collection) show much less hemolysis even after seven years' storage—90 percent recovery and 90 percent 24-hour post transfusion survival.

Advantages of Frozen Red Cells

There are several advantages in the use of frozen red blood cells:

- Longer shelf-life permits a dependable back-up supply of blood when ACD blood is in short demand. Applicability to combat zones is discussed elsewhere.[39]
- Rare blood types may be stored for later autologous or homologous transfusions.
- Hepatitis, if it occurs at all with frozen cells, is rare.[40-42] This is probably related to the extensive washing procedure while preparing the cells.
- Frozen group O negative blood may be stored in quantity and may be safely used as "universal donor" blood, since anti-A and anti-B isoagglutinins and immune globulins are removed during washing.
- Frozen red cells prepared in usual fashion are free of leukocytes and their side effects, probably through destruction during the freezing process with subsequent elimination during the rinse procedures. Frozen red cells are therefore the transfusion of choice for potential organ transplant recipients, as the risk of stimulating the histocompatibility locus antigen (HL-A) system is much less. Many potential kidney recipients are now given frozen red cells for transfusion needs prior to and subsequent to transplantation. Nonspecific leukocyte febrile reactions should be eliminated with the use of frozen blood.
- A variety of erythrocyte enzymes are better preserved in frozen stored red cells than by other

methods.[23] Thus, the low 2,3-DPG levels seen in ACD-stored blood are not a problem with frozen stored blood.

Disadvantages of Frozen Red Cells

There are also disadvantages of the frozen cells:

- Time in preparation is considerable—in roughest estimate perhaps one hour per technologist per five units of cells.
- Preparation and storage space is considerably greater than for ACD blood.
- The potential damage of small amounts of cryoprotective additives must be considered, though even in multiply transfused persons no serious problems have been encountered.
- Most importantly, the cost of frozen red cells remains high—perhaps $50 a unit against about $15 a unit of ACD-stored blood. Efforts to reduce this cost through optimum use of components (platelets, Factor VIII and Factor VIII-poor plasma) separated from the cells before freezing, and through overall increased use of frozen red cells with concomitant improved efficiency in technologists' time, are discussed elsewhere.[43]

Frozen red cells may well represent the safest and highest quality form of red cells available. The cost of preparation may well represent the major stumbling block in widespread use. The relative merits of non-freeze methods for longer shelf-life (CPD, etc.)—for example, ease of preparation and low price of the product—and the merits of frozen blood, such as low incidence of hepatitis and the ability to store rare types, are such that it is likely that both of these methods will be adopted on a much broader scale shortly.

Blood Component Therapy

Whole blood may be thought of as being composed of five basic components, red blood cells, white blood cells, plasma and plasma proteins, coagulation factors, and platelets. Each has a specific purpose and each is now available. By using components the undesirable side effects of whole blood can be minimized, specific factors for specific deficiencies can be given, and the cost of transfusion therapy can be reduced.

Red Blood Cells

The indication for red blood cell transfusion is support of tissue oxygenation. It has been shown that emergency restoration of depleted blood volume can be accomplished with lactated Ringer's solution alone.[44] Earlier use of transfusion as a "tonic" for fatigued patients or to maintain the hemoglobin at some arbitrary level is not indicated and is potentially dangerous. There is no evidence that wound healing or postoperative course is improved by transfusion.[45] The use of single unit transfusions has been cited as an indication of inefficient blood usage. Whole blood may be used for the treatment of acute, life-threatening hemorrhage[46] but lesser degrees of blood loss are best managed with fluids and concentrated red blood cells.[47] The use of whole blood in the treatment of anemia without hypovolemia cannot be justified.

Concentrated Red Blood Cells

The overwhelming majority of red cell transfusions should be given as concentrated red cells (packed red cells or PRC). The American Medical Association Committee on Transfusion and Transplantation states that 60 to 80 percent of all transfusions should be given as PRC,[48] whereas other experts feel that over 80 percent of tranfusion needs should be met with PRC.[49] Indeed the amount of PRC transfused versus the amount of whole blood transfused may be taken as a measure of both proper patient care and maximum blood utilization.

Preparation. PRC are prepared at 4°C by either centrifugation or sedimentation. Red cells more than six days after collection are fragile and must be prepared by sedimentation. PRC are prepared to a hematocrit of 70 percent and have a shelf-life equal to that of whole blood (21 days). PRC so prepared have the same post-transfusion survival and the same cost as the red cells in whole blood.

Advantages. The desirability of using PRC is twofold: PRC are the cornerstone of economical and efficient blood utilization and because of the removal of most of the plasma, use of PRC is associated with the fewest side effects. Some of the side effects so minimized are as follows:

- The chance of circulatory overload is greatly reduced by using PRC. This is especially important in patients with cardiovascular disease.
- There is less chance of a transfusion reaction from antibodies in the donor unit.
- There is less chance of an allergic reaction from plasma proteins or allergens. From 50 to 70 percent of multiply transfused patients receiving whole blood develop antibodies to human gamma globulin.[50]
- Since PRC contain less sodium, potassium,

TABLE 2.—*Differences in Contents Between Packed Red Cells and Whole Blood**

	Packed Red Cells	*Whole Blood*
Volume	300 ml	520 ml
Total hemoglobin	30 grams	30 grams
Hematocrit (Hct.)	70 percent	39 percent
Citrate	22 ml	68 ml
Plasma sodium	15 mEq	45 mEq
Plasma potassium	4 mEq	15 mEq
Plasma acid	25 nanogm	80 nanogm
Plasma ammonia	680 mcgm	2159 mcgm
Immediate effect	3.6 percent rise in Hct.	1.8 percent rise in Hct.

*Modified from Manual of Blood Component Preparation.[53]

acid, citrate and ammonia, the likelihood of toxic side effects from these substances is greatly reduced. This is especially important when dealing with patients with cardiac, renal or hepatic disease.

- Since most of the anti-A and anti-B isoantibodies have been removed, group O PRC are a more satisfactory source of "universal donor" blood.
- Finally, it has been suggested that the risk of hepatitis may be less with PRC.[51,52]

Table 2 summarizes some of the differences between PRC and whole blood.

Leukocyte Poor Packed Red Cells (LPPRC)

Reactions to donor leukocytes are not uncommon and are manifested by fever, chills or other allergic reactions.[54] The reaction is a reflection of antigenic stimulation of the recipient by antigens present on donor leukocytes with subsequent antibody production. The situation is analogous to that of the Rh-negative person exposed to Rh-positive blood, either through pregnancy or transfusion. About 19 percent of women with two pregnancies and 24 percent of women with four or more pregnancies will develop anti-leukocyte antibodies.[55] About 50 percent of patients with 25 or more transfusions will develop significant leukoagglutinins.[56] Prevention of transfusion reactions in patients with anti-leukocyte antibodies may be accomplished with the use of LPPRC.

Preparation. Since, with standard methods of PRC preparation, removal of more than 80 percent of the leukocytes is impossible,[57] a variety of of special techniques have been devised. In preparing LPPRC, blood less than 24 hours old must be used since leukocytes tend to clump on storage, preventing adequate removal. The preparation methods currently used are inverted centrifugation, nylon filtration, dextran sedimentation and saline washing.[3] Inverted centrifugation ("buffy coat poor" red cells), in which the donor bag is inverted and centrifuged, allowing the red cells to be transferred to a satellite bag, is most commonly used, for it has the advantages of sterility in preparation, simplicity, low cost, and a shelf-life of 21 days. It is the least efficient of the methods, however, and 20 to 25 percent of the erythrocytes are left behind in the preparation. The other methods are more efficient but also more costly and time-consuming. Because the "closed system" is entered, there is an increased risk of contamination and the unit must be used shortly after preparation. Saline washing is probably used most commonly when units prepared by inverted centrifugation are not effective in preventing reactions.

Use of LPPRC. Because of the above considerations LPPRC should not be used in place of PRC. LPPRC should be used only in cases where leukoagglutinin transfusion reactions have occurred or in cases where it is especially desirable to prevent the development of anti-leukocyte antibodies[58] as in patients awaiting organ transplantation. When needed, LPPRC prepared by centrifugation should be used, primarily because of lower cost. Should leukoagglutinin reactions still occur, saline washed cells should be used. It should be remembered that frozen red cells are leukocyte-free and may be used instead of LPPRC, if available and competitively priced.

Autologous Blood Transfusion

The advantages of transfusing a patient with his own blood (autologous or autotransfusion) are obvious. The two main complications of homologous transfusion (iso-immunization and transmission of disease, especially hepatitis) are avoided. In addition, patients who object to homologous transfusion on religious grounds may agree to autotransfusion instead.

Autotransfusion has been used in isolated cases for over 100 years[59] and in 1962 the feasibility of withdrawing two units of blood from a patient before operation so that it can be given to him later was shown.[60] Since that time, the ability of a patient to donate up to four units of blood before operation[61] or in anticipation of obstetrical complications[62] has been demonstrated. With the advent of frozen blood storage it is now possible for even severely anemic patients to donate a significant amount of blood which can be held for years for their future use.[63] In addition to obstetrical surgery,[62,64] autotransfusion has been used

successfully in pulmonary[65] and cardiovascular[61] surgery. Methods are being developed for the intra-operative salvage of blood for use in autotransfusion.[59,66,67] Although it is usually not possible for a patient to serve as his own donor, when it is possible it should be encouraged.[68]

Massive Blood Transfusions

The patient receiving massive amounts of blood (more than ten units) over a relatively short time is subject to a number of special problems, including citrate and potassium toxicity, bleeding tendencies, and hypothermia. Other problems such as hypervolemia and post-transfusion hepatitis are discussed elsewhere in this paper.

Citrate toxicity, manifested by gross muscle tremors and typical electrocardiographic changes may be due to secondary hypocalcemia, direct citrate toxicity or both.[69] It is a problem largely restricted to infants subjected to exchange transfusion, may be prevented with the use of packed cells and saline solution, and may often be corrected with intravenous calcium. A common procedure now in use is the prophylactic administration of 10 ml of 10 percent calcium gluconate for every four to six units of whole blood, not given in the blood itself, else clotting will occur immediately. Hyperkalemia of significant degree is uncommon in massively transfused patients unless underlying renal damage is present.[69,70] Hyperkalemia may be prevented through the use of packed cells or fresh blood.

Bleeding tendencies frequently occur in the face of massive transfusions, especially in the postsurgical or trauma patient. It is imperative to eliminate a surgical or traumatic cause of bleeding before embarking on an extensive hemostatic evaluation. Appearance of purpura or bleeding from multiple venipuncture sites suggests a transfusion-acquired problem. Evaluation should include a platelet count and determination of bleeding time, prothrombin time, partial thromboplastin time and thrombin time. The most likely causes include dilutional thrombocytopenia, Factor V or VIII deficiency (which occurs as a result of use of whole bank blood deficient in these factors), hypocalcemia, and intravascular coagulation (which of course is the result of the patient's disease rather than the transfusion per se). A recent study documents the rarity of bleeding if fewer than 20 units are transfused, and the relationship between progressive abnormalities in the prothrombin time and platelet count and increasing number of units transfused.[71] The occurrence of bleeding correlated best with thrombocytopenia (about 65,000 per cu mm) and was corrected with fresh whole blood, but not fresh frozen plasma. In acutely ill, multiply transfused, bleeding patients it would seem prudent after drawing appropriate studies to treat with fresh blood (or platelet packs and fresh plasma, which contains Factors V and VIII) and calcium until a firm determination of cause can be reached.

Hypothermia as a result of massive transfusion with cold blood has been well documented, with esophageal temperatures as low as 28°C recorded.[69] The apparently increased risk of cardiac arrest in these instances should be avoided by warming the blood before transfusion, usually with the use of a heated coil or water bath, with careful attention to avoid overheating.

It should be emphasized that, when indicated, massive transfusion is life saving while most of the complications thereof are relatively uncommon and even when present are fairly readily treatable. The possibility of such complications should not influence the decision to transfuse massively when there is a need for such therapy.

White Blood Cells

The major indication for leukocyte transfusion is life-threatening leukopenia, as often occurs in patients with leukemia who are receiving chemotherapy. Unlike platelet transfusion, leukocyte transfusions are still fraught with difficulty and for the most part are used only in research centers. Following transfusion, leukocytes rapidly leave the circulation so that after one hour only about 5 percent of transfused leukocytes are detectable. Approximately 1×10^{11} leukocytes are needed to raise the leukocyte count by 1,000 per cu mm.[72] This is more leukocytes than normally are circulating at any one time (a 70-Kg man has about 2.5×10^{10} to 5.0×10^{10} circulating leukocytes). Despite these problems, methods have been devised for leukocyte transfusion and used with some success.

Preparation. The most common method of preparation of leukocytes for transfusion is by plasmapheresis, the white cells being processed for transfusion while the red blood cells are returned to the donor. By repeating this process, multiple "units" of white blood cells may be donated with minimum loss of erythrocytes from the donor. A more detailed explanation of plasmapheresis is available elsewhere.[3] Because huge numbers of

granulocytes must be transfused, patients with chronic myelogenous leukemia (CML) and white counts greater than 100,000 per cu mm have been utilized as donors. Granulocytes from these patients are known to circulate and function normally.[73] The theoretical possibility of transmitting CML to the recipient exists, although no such cases have been reported despite the temporary engraftment of Philadelphia chromosome-positive donor cells in the recipient bone marrow for up to 52 days.[74]

Recently a modification of plasmapheresis, known as filtration leukopheresis, utilizing normal donors has been described.[75] Heparinized donor blood is passed through a siliconized glass wool filter. The alkalinity of the heparinized blood causes the granulocytes to adhere to the filter while the remainder of the unit passes through unaltered and is returned to the donor. The procedure is usually repeated four to five times and then the granulocytes are eluted from the filter by ABO compatible plasma at a more acid pH. In this way, 2,400 ml of whole blood will yield 9.8×10^9 leukocytes, of which 80 percent are granulocytes. A modification of this procedure, using peristaltic pumps for continuous flow operation, has demonstrated that up to 5×10^{10} leukocytes may be collected during a single two and one-half hour collection period.

Automated methods of leukocyte separation have the advantage of allowing rapid and continual separation of leukocytes while returning the unneeded components to the donor. One such method, the continuous-flow blood cell separator, is now available and is able to collect from normal donors an average of 1.5×10^{10} leukocytes, of which 60 percent are granulocytes.[77] If donors with CML are used, the average collection increases to 2.5×10^{11} leukocytes.[77] If donor leukocytes are mobilized with cortisone or etiocholanolone, yields can be further increased by 100 percent.[78]

Use. Several reports indicate that leukocyte transfusions are of benefit in granulocytopenic patients.[72,73,79] One study of 722 patients given leukocyte transfusions showed a significant rise in peripheral white count in 38 percent and a favorable response to infection in 52 percent.[79]

Plasma and Plasma Protein Derivatives

For many years plasma was used as a volume expander or for replacement of coagulation factors or serum proteins. With the development of hepatitis-free, effective volume expanders (for example, Dextran®, albumin, Plasmanate®) the use of plasma has declined.[80] The development of clotting factor concentrates and purified serum proteins has further decreased the need for plasma per se.

Plasma Preparations

Plasma is now available only as single donor units, as multiple donor units ("pooled plasma") have been taken off the market.

Single donor plasma, prepared fresh or frozen within six hours after separation from whole blood, will contain essentially all clotting factors, proteins, and isoantibodies present in whole blood. If free of irregular antibodies it may be given to ABO-type compatible patients without crossmatching; otherwise it must be crossmatched before use. Fresh or fresh frozen plasma may be used for replacement of clotting factors if specific factor concentrates are not available, though the latter are more effective. Plasma over 24 hours old can only be used for volume expansion or for fractionation to plasma protein derivatives. The risk of hepatitis per unit of plasma is the same as that of a single unit of whole blood.

Pooled plasma, now no longer available, was formerly prepared from eight to twenty donors, stored at 34°C for six months and irradiated with ultraviolet light to inactivate hepatitis virus.[81] During World War II and the Korean conflict, plasma preparations made from larger pools (50 to 200 donors) were associated with hepatitis infectivity rates of 7.5 percent and 21 percent[82] since a single infected donor contaminates the entire pool. Plasma from smaller donor pools was also found to have an unacceptably high hepatitis risk as well as unacceptably high titres of "immune" anti-A and anti-B.[83,84] Following recommendations from the Committee on Plasma and Plasma Substitutes, National Research Council[85] pooled plasma was disapproved for use.

Plasma Protein Derivatives

The development of the Cohn fractionation process has resulted in the purification of various plasma proteins: albumin, gamma globulin, and fibrinogen.

Albumin is the primary colloid of plasma. It is heat-stable and so can be rendered free of hepatitis by heating to 60°C for ten hours. It is a safe and effective volume expander. Purified albumin

is available in two concentrations, 5 percent albumin which is essentially iso-osmotic with plasma, and 25 percent albumin which is useful in treating shock in the absence of dehydration, or in treating hypoalbuminemia. In the latter instance, it is important to recognize that relatively large doses of albumin must be used, as it may be calculated that approximately 35 grams of albumin are needed to raise the plasma albumin by one gram per 100 ml.

Plasma protein fraction, USP (PPF, Plasmanate®) is a by-product of Cohn fractionation for gamma globulin and fibrinogen. It is composed of 88 percent albumin, 7 percent low molecular weight alpha globulin, and 5 percent low molecular weight beta globulin in saline solution. It offers no advantage over albumin alone.[86] Like albumin it is heat-treated to destroy the hepatitis virus. PPF does not contain any clotting factors and so can only be used as a volume expander. As the isoantibodies have been removed, it can be given without typing or crossmatching.

Gamma globulin is available in two forms, immune (pooled) and hyperimmune. Several recent reviews discuss the use of gamma globulin in greater detail.[87-89] Gamma globulin is apparently free of the hepatitis virus.[90]

Pooled or immune serum globulin, prepared from normal donors, is used in the treatment of antibody deficiency states and for the prevention of rubeola, infectious hepatitis, and poliomyelitis. Since IgG antibodies have a half-life of 20 to 25 days, gamma globulin when used for deficiency states should be administered every two to four weeks. Its use in the prophylaxis of rubella in pregnant women is uncertain.[87] The use of immune serum globulin intramuscularly has been thought to be of some value in the prevention of post-transfusion hepatitis[91] but recently a large, prospective, controlled study showed it to be of no value at all.[92] A study of gamma globulin specifically modified for intravenous use, in which the globulin was directly added to the unit of blood *in vitro,* has shown a decrease in the number of icteric (but not anicteric) cases of post-transfusion hepatitis.[93] It should be emphasized that gamma globulin as commercially supplied cannot be used intravenously.

Hyperimmune serum globulin is prepared from hyperimmunized or convalescing donors with a high titre of a specific antibody. Thus there are individual preparations, each for a specific diseasc. Hyperimmune serum globulins have been shown to be of value in the prevention of mumps, pertussis, tetanus, and vaccinia. Recently a preparation with a high anti-hepatitis associated antigen (HAA) titre has been shown to be effective in preventing endemic HAA-positive hepatitis.[94]

Gamma globulin is also used in the prevention of erythroblastosis fetalis. Preparations of anti-Rho gamma globulin (RhoGAM®) obtained from Rh-negative women immune to the Rho antigen are commercially available and widely used. When given to an Rh-negative mother within 72 hours following delivery, miscarriage or Rh incompatible transfusion, the globulin attaches to and helps destroy circulating Rh-positive erythrocytes, thus preventing an immune response in the mother. Sensitization of the mother with subsequent erythroblastosis fetalis in the next pregnancy is thus avoided.

Coagulation Factors

In the past, all deficiencies of blood clotting factors were treated with fresh blood or plasma. Although effective, such therapy had the major disadvantage of requiring large volumes, and hypervolemia was often a result, sometimes preventing the achievement of adequate levels of the deficient factor. In addition, a certain amount of red cell contamination was inevitable and iso-immunization often resulted.[89] The development of specific component therapy largely corrected these problems and today three such components are available, Factors VIII, IX and I.

Factor VIII Preparations

Hemophilia A (Factor VIII deficiency, AHG deficiency, AHF deficiency, classical hemophilia) is due to a congenital Factor VIII deficiency (antihemophiliac globulin or AHG, antihemophiliac factor or AHF). The site of Factor VIII synthesis is unknown, the spleen, liver, bone marrow, kidney, reticuloendothelial cells, plasma cells, lymphocytes, macrophages, and fibroblasts all having been implicated.[4] Detailed discussions of clinical aspects of hemophilia are available elsewhere.[95,96] Factor VIII activity* is usually expressed as a percentage, the average being 100 percent with a usual range of 50 to 200 percent. Severe hemophiliacs have Factor VIII level of less than 1 percent. Milder hemophiliacs who have 5 percent or more Factor VIII may have little trouble. Factor VIII has a

*One unit of Factor VIII activity is defined as the amount of Factor VIII activity present in 1 ml of normal plasma.

short half-life of eight to twelve hours both *in vivo* and *in vitro* and so must be obtained from fresh plasma. At present two forms of Factor VIII preparations are widely used in this country: cryoprecipitate and glycine-precipitated Factor VIII. Fresh plasma should not be widely used, as is discussed elsewhere.[4]

Cryoprecipitate. In 1959 it was noted by chance that during the administration of fresh frozen plasma to hemophiliacs a significant amount of Factor VIII activity remained in the bottle along with cold precipitated fibrinogen.[97] From this observation came an easy and inexpensive method of preparing a Factor VIII concentrate, known as cryoprecipitate.[98] Platelet poor plasma is rapidly frozen to −70°C and then thawed at 4°C in a refrigerator overnight. A "sludge" will remain (the cryoprecipitate) which contains Factor VIII and fibrinogen. The thawed plasma is then expressed into a satellite bag (cryoprecipitate-poor plasma) and may be used as a volume expander or further fractionated. The cryoprecipitate remaining is then used or may be refrozen and stored at −30°C for many months. When so prepared about 50 percent of the original Factor VIII activity will be recovered in the cryoprecipitate, each bag containing about 80 to 90 units. The cost per Factor VIII unit is about 7 cents for cryoprecipitate.[99] It has proved to be effective for most bleeding episodes in hemophiliac patients.[100,101]

Glycine-precipitated Factor VIII. For hemophiliacs who must undergo surgical operation, who have life-threatening hemorrhage (e.g., CNS, gastrointestinal, or around major airways), or who have high levels of anti-factor VIII antibodies (see below), very high doses of Factor VIII must be given, making cryoprecipitate less desirable. For these patients a more concentrated preparation, glycine-precipitated Factor VIII, is available.[102] Glycine is used to precipitate a Factor VIII rich protein fraction from pooled fresh plasma. The precipitate is dissolved in a citrate-saline solution and lyophilized. It may be stored up to one year and is reconstituted immediately before use. Unlike cryoprecipitate, the concentrate is assayed for potency, each vial containing 200 to 300 Factor VIII units. Unfortunately, both the cost (10 to 16 cents per Factor VIII unit)[99] and the risk of hepatitis are higher than with cryoprecipitate. It has been proved to be an effective treatment for hemophilia A.[103]

Use of Factor VIII preparations. An excellent review of the management of hemophilia has been published.[4] A few points regarding therapy with cryoprecipitate or Factor VIII concentrate will be discussed here.

The principle in replacement therapy is to raise the Factor VIII to levels adequate to achieve hemostasis. The level needed depends on the severity of the condition. It has been stated that a level of 5 to 20 percent of normal is adequate for spontaneous bleeding, 20 to 40 percent of normal for injuries and minor surgical procedures, and 80 to 100 percent of normal during major operations.[104,105] The dose of Factor VIII needed to achieve a given level may be calculated from the patient's weight.[4,106] Because of its short half-life, Factor VIII must be given every eight to twelve hours. If twice the minimum calculated dose is given initially and then the minimum dose repeated every 12 hours, the Factor VIII level will remain above the minimum desired level. Factor VIII must be given intravenously, the intramuscular administration having been shown to be ineffective.[107]

Minor hemorrhages may often be treated by single large Factor VIII infusions,[108] thus allowing home treatment programs.[109,110] Prophylactic treatment programs have also proven effective and safe, provided expert hematologic supervision is available when needed.[110-112] The yearly cost of care for a hemophiliac may be reduced from about $10,000 to about $1,000 on the prophylactic program, or to about $400 on the home care program.

Surgical operation and dental care in hemophiliac patients is discussed elsewhere.[113-119]

Complications of Factor VIII preparations. Allergic reactions, such as hives and chills, are common with the administration of plasma, but are uncommon with the Factor VIII preparations. When they occur they should be treated symptomatically with antihistamines.[4]

Hepatitis can be transmitted by all preparations used in treatment of hemophilia. As mentioned previously, the risk is much greater with the glycine-precipitated Factor VIII since it is made from pooled plasma. The problem of hepatitis prevention and treatment is discussed elsewhere in this paper.

Antibodies to Factor VIII develop in about 5 percent of hemophiliacs. Patients given animal Factor VIII develop species-specific antibodies which do not cross react with Factor VIII from other species. Patients with anti-human Factor VIII antibodies may have low activity against the animal Factor VIII preparations and may be treated with them, but will eventually develop the

species-specific antibody. Attempts to neutralize the anti-Factor VIII antibody with massive doses of Factor VIII concentrates have been partially successful, though such efforts may provoke an anamnestic response with late rebound of very high anti-Factor VIII antibodies.[120] Steroids and immunosuppressive drugs have been used in an attempt to lower the anti-Factor VIII titer with variable results.[4]

Factor IX Preparations

Hemophilia B (Factor IX deficiency, PTC deficiency, Christmas disease) is due to a congenital deficiency of Factor IX (plasma thromboplastin component or PTC). Like hemophilia A, from which it is clinically indistinguishable except for a higher proportion of milder cases, hemophilia B is transmitted as a sex-linked recessive trait. Hemophilia B is much rarer than hemophilia A, and must be diagnosed by specific clotting factor analysis. More complete descriptions of hemophilia B are available elsewhere.[95,96]

Unlike Factor VIII, Factor IX is more stable *in vitro* and therefore stored blood or plasma three weeks old may be used as a source of Factor IX. Factor IX has a longer half-life (24 hours) than Factor VIII. Actually, when Factor IX is infused the disappearance curve is biphasic, the first phase having a half-life of about four and a half hours and the second phase having a half-life of about 32 hours. Approximately 50 percent of the Factor IX activity present *in vitro* is recovered *in vivo*. It is thought that the first phase of the disappearance curve represents equilibration in the extravascular space. It has been shown that Factor IX has an apparent volume of distribution of 2.7 times the plasma volume.[121] Factor IX is available as Factor VIII-poor plasma and as the commercial concentrate. The latter product is much more satisfactory in the treatment of hemophilia B. It should be noted that cryoprecipitate contains no Factor IX.

Factor IX concentrate is prepared from the effluent of Cohn fraction I (fibrinogen) by absorption on diethylaminoethyl (DEAE) sephadex and fractional elution. It also contains Factors II, VII and X (the vitamin K dependent factors or "prothrombin complex"). It is dispensed into vials and lyophilized. Each vial is reconstituted with sterile water before use[121] and is assayed, each vial containing 500 units of Factor IX activity. It has been shown to be effective in the management of hemophilia B.[121-123] The cost per Factor IX unit is about 14 cents.[99]

Use of Factor IX concentrate. The principles in the treatment of hemophilia B with Factor IX concentrate are the same as in the treatment of hemophilia A with Factor VIII. There are several practical differences, however. Because of the longer half-life of Factor IX, it is given every 24 hours. It must be kept in mind that the *in vivo* recovery of Factor IX is only about 50 percent, so the number of units of Factor IX given will be about twice that for Factor VIII.

Because Factor IX concentrate also contains Factor II, VII, and X, it has been successfully used in the treatment of deficiencies of these clotting factors caused by severe hepatic disease or excessive oral anticoagulant ingestion.[124] It should be noted that the incidence of hepatitis from Factor IX preparations is quite high (see below).

Fibrinogen (Factor I)

Fibrinogen is prepared from pooled plasma by Cohn fractionation. The risk of transmission of hepatitis by fibrinogen is high, being reported as 6 to 35 percent in various series and even over 50 percent in one series.[125]

The main use of fibrinogen is for replacement in conditions with absent or low fibrinogen. Congenital afibrinogenemia is a very rare condition, only slightly more than 60 cases having been reported. It is characterized by an almost total absence of fibrinogen. Spontaneous hemorrhages and hemarthroses are rare, most bleeding being post-traumatic, and for this reason prophylaxis is not recommended.[126] It is inherited as an autosomal recessive with the heterozygote showing a consistently low fibrinogen level (so called "congenital fibrinogenopenia").[127] Acquired hypofibrinogenemia, on the other hand, is much more common. It occurs in three clinical settings: decreased production (as in severe hepatic disease), disseminated intravascular coagulation or fibrinolysis or both (all the hypofibrinogenemias associated with complications of pregnancy belong to this group),[128] and dysfibrinogenemias (production of an abnormal fibrinogen no longer clottable by thrombin).

Fibrinogen has been shown to be effective replacement therapy in patients with congenital afibrinogenemia and in patients with severe hypofibrinogenemia secondary to severe liver disease.[129] It has been pointed out, however, that cryoprecipitate (which contains fibrinogen) with its lower risk

of hepatitis transmission and despite its higher cost can and possibly should be used in the treatment of congenital hypofibrinogenemia.[130,131] The use of fibrinogen in hypofibrinogenemia associated with disseminated intravascular coagulation is not necessary and may even be harmful.[132] It is the opinion of some investigators that the only indication for the use of fibrinogen is congenital afibrinogenemia[133] while others feel there is no clinical use for fibrinogen at all.[134]

Platelets

Thrombocytopenia is the most common cause of clinical bleeding states and may be caused by platelet underproduction or by excessive platelet destruction. In addition, qualitative platelet defects (Glanzman's disease, primary platelet dysfunction, and others) are occasionally encountered as the cause of a bleeding diathesis. Platelet transfusions frequently offer the most direct mode of therapy in cases of platelet underproduction and are therefore in constant demand. Recent reviews summarize morphologic and physiological aspects of platelets.[135,136]

Indications

Platelet transfusions are of most benefit in production deficient syndromes—for example, aplastic anemia and leukemia. In these and similar disorders the platelet count may be used as a rough estimate of the need for platelet transfusion. Serious bleeding is uncommon with platelet counts greater than 20,000 per cu mm, indeed "gross hemorrhage occurred on 30 percent of hospital days . . . when the platelet count was less than 1,000 per cu mm, but on less than 1 percent of the days when the count was 20,000 to 50,000 per cu mm."[2] A platelet count of less than 20,000 could therefore be used as indication for platelet transfusion though in practice it is usually unnecessary to transfuse platelets until counts reach 10,000 to 15,000. Indeed, even in these cases it is often expedient to await early signs of bleeding before starting platelet transfusions, as transfusion will eventually result in appearance of shortened post-transfusion platelet survival.

The use of platelet transfusion in platelet destruction syndromes (for example, idiopathic thrombocytopenic purpura) is far less beneficial and should be reserved for true emergencies or, possibly, surgical operation.[2] In patients with ITP who must undergo splenectomy, for example, it is often advantageous to give platelets just before or during operation, especially if the platelet count is less than 40,000 to 50,000 or the bleeding time is prolonged.

Preparation and Storage

Platelets may be given in fresh whole blood or as platelet-rich plasma or platelet concentrates. Because of smaller volume and relative purity, concentrates are used almost exclusively today.

Platelet concentrates must be prepared from ACD preserved blood as heparin causes platelet clumping and EDTA appears to cause toxic and morphologic changes. Each unit ("pack") prepared will contain approximately 0.7×10^{11} platelets,[2,137] or about 20 percent fewer platelets than were originally present in the unit of blood.

Initially, because of experience with red cells, platelet preparation and storage was at 4°C. Subsequently it was demonstrated that lower temperatures exerted a detrimental effect on platelets, manifested by platelet aggregation, change in shape, and centripetal movement of subcellular organelles.[138-140] It was demonstrated that after eighteen hours' storage at 4°C platelets could be recovered in a yield of 42 percent with a half-life *in vivo* survival of 1.3 days compared with 55 percent and 3.9 days, respectively, at room temperature (22°C).[138] For this reason, most centers now store platelets at room temperature though initial centrifugation during preparation is often at 4°C. Acidification of platelets with ACD to prevent aggregation is apparently not needed at the warmer temperature and is not performed at most centers today, although the platelets are agitated within the pack to help prevent aggregation.[142] A recent study indicates that platelets stored at the lower temperature, while showing lower *in vivo* recovery after transfusion, result in more shortening of the post-transfusion bleeding time and better hemostasis.[143] More studies are indicated to better define optimum storage conditions for platelets.

Studies of bacteriologic sterility in platelet packs stored at 22°C are somewhat conflicting[144-146] but seem to indicate that a small number of units stored for longer periods do show bacteriologic proliferation and may cause sepsis in the recipient. It is therefore recommended that freshly drawn platelets be used whenever possible, and that stored units be used only when the former are not available.

Storage of platelets in the frozen state has been achieved,[141] but post-transfusion *in vivo* recovery

is poor (30 to 50 percent).[147,148] Dimethylsulfoxide and dextrose are used as cryoprotective agents, though a recent study[149] in which dimethylacetamide and dextrose were used points to advantages inherent in the latter agents. At present these methods must be considered investigational and too expensive for general use.

Administration

Platelets prepared and stored as outlined above may be used effectively for up to 96 hours after donation, though with progressively diminishing recovery. However, the Division of Biologic Standards recommends use within 24 hours of donation.

The desired number of platelet units (usually four to ten) are pooled just before administration and are given intravenously fairly rapidly, often by syringe. There is some controversy regarding the desirability of using platelet filters, with a relative dearth of information to document any position. A single study of standard whole blood filters used to filter platelets indicated only a 3 percent loss during filtering, with normal *in vivo* platelet survival.[150] However, use of standard blood filters and tubing for administration of platelets is unwise due to rather large losses of platelets in the delivery system. For this reason, a number of platelet filters are now commercially available and widely used. We are unable to find written documentation of their efficacy, nor are their manufacturers able to supply conclusive evidence on that point.[151] Even so, it would seem prudent to use the filters to prevent the possible but rare case of particulate embolism.

Post-Transfusion Survival and Platelet Antibodies

Post-transfusion platelet survival varies tremendously with the diagnosis of the recipient, the presence or absence of fever or bleeding, development of platelet antibodies, and individual variation. Under optimum conditions, and with infusion of freshly drawn platelets, a one-hour *in vivo* yield of about 70 percent may be expected.[138] This immediate yield will decrease by about 15 to 20 percent per day of storage though subsequent *in vivo* survival will remain fairly constant. A usual figure given for platelet count increment following transfusion is 10,000 per cu mm platelets per square meter of body surface area per platelet pack.[137] Hence an adult will require approximately four platelet packs to raise his platelet count by 20,000, though in many cases considerably more will be needed. Under optimum conditions the half-life for transfused platelets is perhaps four days, though in cases of idiopathic thrombocytopenic purpura the half-life may be less than one hour.

Platelet requirements are often noted to increase over a period of time in patients requiring repeated platelet transfusions. Post-transfusion survival of platelets is noted to be considerably shortened, the reason for which apparently lies in the formation of anti-platelet antibodies.

The platelet antigen system, like the red cell system, is complex. However, it is apparently the HLA "histocompatibility" antigen system which accounts for the progressive increase in platelet requirements in multiply transfused patients.[152] In multiply transfused patients with aplastic anemia unresponsive to platelets from random donors, striking responses were noted to transfusion with HLA-compatible platelets, allowing support for many months.[152] Such responses have also been noted in acute leukemia.[153] Should HLA typing become available on a large scale, more intelligent use of platelets should result. Until then, platelet transfusion should be given only when absolutely indicated to prevent early development of platelet antibodies.

Transfusion of ABO incompatible platelets has been shown to decrease post-transfusion survival, though this is disputed.[154] Rh incompatible platelet transfusions do not alter survival though Rh isoimmunization through contaminating red cells may occur. The risk of immunization seems, however, to be quite low (about 8 percent),[154] perhaps in part due to the fact that many of the recipients are also receiving immunosuppressive therapy.

In summary then, ABO-Rh compatible platelets should be given, but if shortages of Rh negative platelets arise, Rh negative patients may receive Rh positive platelet transfusions. For patients who may require repeated platelet transfusions over many months, consideration may be given to HLA typing.

Hepatitis

It has been estimated that following transfusion each year 30,000 cases of icteric hepatitis, 90,000 to 150,000 cases of anicteric hepatitis and 1,500 to 3,000 hepatitis-related deaths occur in the United States.[155] Since therapy of hepatitis is at best supportive, it is of great practical concern to prevent transmission. The recently acquired knowl-

edge of the association of the Australia antigen with hepatitis makes it possible to diminish the incidence of post-transfusion hepatitis by perhaps 25 percent to 40 percent.[156]

Hepatitis Associated Antigen

The hepatitis associated antigen (HAA, Australia Antigen, Au) was found initially in the serum of an Australian aborigine which, in 1963, was found to react with a newly discovered antibody in the serum of a multiply transfused hemophiliac.[157] HAA now appears by electron microscopy to consist of several particles: spheres and tubules of about 200 Angstroms diameter and a larger complex particle (Dane particle) of about 400 Angstroms. It is hypothesized that the virus itself, probably a rhinovirus, lies at the core of the Dane particle, and that the outer coat of the Dane particle as well as the spheres and tubules represent virus coat protein. It is apparently this virus coat protein that is the true hepatitis-associated antigen to which antibodies are formed.[158] The viral nature of HAA and its association with hepatitis, hepatoma and other disorders is discussed elsewhere.[159,160]

Risk of Post-Transfusion Hepatitis

The risk of transfusion hepatitis varies considerably with the donor population[161-164] and the blood component used in transfusion.[52,125,165,166] Commercially obtained blood carries a tenfold higher risk of hepatitis than blood from volunteers: among paid donors, approximately 1 to 5 percent of whole blood units will result in clinical hepatitis, while among unpaid donors anywhere from 0.1 to 0.3 percent of blood units will result in clinical hepatitis. In addition, anicteric (subclinical) hepatitis probably occurs three to ten times as frequently as the clinical type.

Mollison states that as little as 10^{-6} ml of infected plasma may cause hepatitis.[165] Thus, for practical purposes any blood product containing plasma may be considered capable of causing hepatitis. Only albumin, thrombin, fibrinolysin, globulin and possibly frozen red cells are considered free of the virus.[167] Table 3 summarizes the risks involved.

Obviously, pooled products from multiple donors carry increased risk since one infected donor will contaminate the pool. Transfusion hepatitis incidences of 10 to 50 percent have been reported with some pooled plasma specimens and preparations of Factor IX concentrates or fibrinogen.[125,166] Plasma protein fraction, albumin, thrombin and fibrinolysin are free of hepatitis virus because of prolonged heat treatment, a procedure which would denature the proteins of whole plasma. Frozen red cells appear to be free of infectivity, probably because of the separation of plasma and extensive washing during preparation, and using them is the best way of avoiding post-transfusion hepatitis (see frozen red cells). Packed red cells may carry a slightly lower risk than whole blood, perhaps because of removal of most of the plasma.[51,52]

Hepatitis Screening

Attempts to eliminate transfusion hepatitis through elimination of infected donors have been repeatedly made. Early efforts to screen donors on the basis of liver function tests proved fruitless, as mild abnormalities eliminated from 30 to 50 percent of the donor pool with a reduction in hepatitis of about 50 percent.[165] Recent efforts to screen for HAA in donor blood seem more promising. It has been demonstrated that approximately 42 percent of patients transfused with HAA-positive blood develop clinical hepatitis, with about 75 percent developing hepatitis, HAA antigenemia or anti-HAA.[156] Since only 0.1 percent of volunteer donors, or 1 percent of paid donors, are HAA-positive,[168,169] one would expect that elimination of the small number of HAA-positive donors would prevent a fair percentage of cases of hepatitis—estimates vary from 25 percent to 40 percent.[156,170] These figures may improve with more sophisticated methods of detecting HAA, for at present well documented cases of hepatitis from HAA-negative donors have been recorded, implying either insensitive techniques of detection or another etiologic agent, or both.[156]

TABLE 3.—*Relative Risk of Hepatitis Entailed in Use of Various Blood Products*

Low Risk	*Average Risk*	*High Risk*
Frozen Red Cells	Whole Blood	Factor VIII Concentrate
Plasma Protein Fraction	Packed Red Cells	Factor IX Concentrate
Albumin	Single Platelet Unit	Pooled Plasma
Gamma Globulin	Cryoprecipitate	Fibrinogen
Autologous Blood	Single Donor Plasma	

All large centers screen all blood units for HAA; indeed legally there may be no alternative. Several methods for detecting HAA are available and include agar gel diffusion, immunoelectroosmophoresis (IEOP), complement fixation and a radioimmune assay. Detailed discussion of these tests is beyond the scope of this paper and may be found elsewhere.[94,168,171,172] Perhaps the most widely used method today is IEOP. It is simple, rapid (90 minutes per several hundred samples) and relatively inexpensive (25 cents per sample). However, it is probably not as sensitive as either complement fixation techniques or a recently described radioimmune method[94] and is likely to be supplanted by these methods. In all cases, positive donor units are discarded and the donor notified of the presence of HAA in his blood. Subsequent management of these donors is discussed in detail elsewhere.[170]

Despite the extensive technology in this field, it has been suggested that the best way to eliminate transfusion hepatitis is simply to eliminate units obtained from paid donors,[156] though this is impossible at present since the supply of volunteer donors is insufficient to meet demands.

In summary, hepatitis prevention is of primary importance. Blood from volunteer donors should be given preference over that from commercial donors; pooled plasma and coagulation factors should be administered only when absolutely indicated, preferably under the direction of a hematologist; HAA screening of all blood obtained should be made and HAA-positive units removed; finally, blood transfusions should be given as packed or frozen cells, rather than whole blood, and then only when absolutely indicated.

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Important Advances in Clinical Medicine

Epitomes of Progress— Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Preventive Medicine and Public Health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Preventive Medicine and Public Health which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

California Moves for Control of Salmonellosis Associated with Pet Turtles

NUMEROUS STUDIES during the past ten years have shown that small pet turtles can be an important source of salmonellosis in humans. Cold-blooded animals can harbor many of those salmonella serotypes known to infect man and animals. Commercially raised turtles usually are fed salmonella-contaminated animal products. The salmonella infection can then be transmitted to their young. Salmonella organisms are often recovered from turtles and turtle tanks in pet stores and homes.

The Department of Health, Education and Welfare estimates that 15 million pet turtles are sold each year in this country and that 90 percent of them are raised in domestic turtle ponds. HEW also estimates that as many as 300,000 cases of turtle-borne salmonellosis occur each year in the United States. To be sure, salmonella organisms can come from many other sources but the opportunities for spread by contaminated pet turtles are unique. For example, most people do not think of these small animals as literally bathing in their own excrement. Turtle tanks are often kept or cleaned in the kitchen increasing the risk of contaminating food preparation areas. Turtles are most often given to children who cannot comprehend the precautions necessary to prevent infection, and who are most susceptible.

Attempts to control the problem by raising turtles in salmonella-free environments have been disappointing; there are simply too many opportunities for contamination to occur before the turtles are purchased at retail outlets. A few state and local governments have adopted regulations setting bacteriologic standards for turtles before their sale or requiring the health officer of the

state in which the turtles are raised to certify them free of salmonella organisms before shipment. In effect, these regulations ban the sale of pet turtles in those areas. The state of Washington, the leader in control procedure of this type, has noted the near disappearance of turtle-associated salmonellosis.

In April 1972, the Food and Drug Administration and the Health Services and Mental Health Administration proposed regulations to restrict the importation and interstate shipment of small pet turtles. These federal level controls should obviate the need for state or local regulations.

In California, regulations, approved on September 15 by the State Board of Public Health of California, will require the state of origin to certify the turtles as salmonella-free by methods that are approved in advance by the California State Department of Public Health. The regulations stipulate that health education be used to alert the public to the potential hazards involved with pet turtles.

Once in effect, these regulations will place our state among the growing list of areas that have moved to control this problem.

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Interpreting Current Serologic Tests for Syphilis

THE VDRL TEST remains the most universal nontreponemal antigen test for syphilis. Although not absolutely specific for syphilis, a reactive result indicates past or present infection. A non-reactive result usually indicates absence of syphilis. Serial quantitative VDRL examinations may reveal a dynamic process. A rising titre may indicate a recent infection, reinfection, relapse or a biologic false (BFP) reaction. A falling titre is a useful indicator of response to therapy.

A single reactive VDRL test does not constitute a diagnosis of syphilis. A repeat test is important. Previous test results, exposure, clinical findings, history of chancre or rash, maternal history of syphilis support the diagnosis.

The VDRL is usually non-reactive until one to two weeks after the appearance of the chancre. Darkfield examination of suspicious lesions is important.

Patients with secondary syphilis develop a high antibody titre, but the VDRL may appear to be non-reactive due to the prozone phenomenon. On all lesion cases, ask the laboratory to dilute the serum and titrate.

Reactive VDRL's from cord blood often represent passive transfer of antibody from the mother. A VDRL should be performed on the infant every month for three months to determine whether the titre is rising or falling. A rising titre indicates need for therapy. A falling titre becoming nonreactive indicates passive transfer, not congenital syphilis.

A reactive VDRL in the absence of syphilis is a biologic false positive (BFP) reaction. A BFP must always be proved not to represent syphilis. It is important to determine the reason for a biological false positive. A multitude of conditions may cause a BFP reaction—acute and chronic disease, immunization, drug use, pregnancy.

Cases with no apparent reason for a reactive VDRL test require an FTA-ABS test. Results of the FTA-ABS are usually conclusive—reactives indicate syphilis, non-reactives do not. Borderline results (weakly reactive, etc.) require follow-up testing. If a patient continues to present a diagnostic problem after repeated VDRL and FTA-ABS tests, TPI testing may aid in the diagnosis.

A reactive VDRL test on a spinal fluid specimen indicates syphilis. Central nervous system syphilis should also be suspected with elevated spinal fluid white blood cell count and total protein.

If the patient receives treatment several years after acquiring syphilis, the VDRL may remain reactive for life. Treatment should not be repeated without evidence of reinfection.

With a previously treated case, a sustained fourfold rise in titre—for example, 1:2 to 1:8—performed by the same laboratory indicates need for retreatment. The major exception is adequately treated congenital syphilis where titres may fluctuate for no particular reason.

Doubt about previous therapy, especially in pregnant women, calls for retreatment.

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Vibrio Parahemolyticus, a Newly Recognized Cause of Food-borne Illness

In the United States the three most commonly encountered causes of food-borne illness are salmonellae infection, Clostridium perfringens, and staphylococcal enterotoxin. More recently, illness from V. parahemolyticus has also been recognized. In Japan it is one of the leading causes of food-borne disease, and recently has been identified as an important pathogen in other countries.

It was first recognized as a cause of food-borne illness in Japan in 1950 when 272 persons developed acute gastroenteritis after consuming sardine larvae; 20 died. In the United States there have been ten reported outbreaks attributed to V. parahemolyticus. The first two were unconfirmed and reported in 1969 from the state of Washington and two more outbreaks were reported from that state in 1970; three confirmed outbreaks were reported from Maryland in 1971 and two more in 1972. An unconfirmed outbreak was reported from Hawaii in 1972. In all of these outbreaks, seafood was identified as the vehicle; food-borne outbreaks of V. parahemolyticus studied elsewhere also have shown exclusive association with seafood.

V. parahemolyticus is an enteropathogenic, Gram-negative, rod-shaped facultative microbe preferring alkaline conditions and a salt concentration of 2 to 4 percent. It appears to be able to live freely in marine waters without an animal host. In the United States the organism has been isolated from fish, crustaceans, and shellfish at Puget Sound on the Pacific Coast; from shellfish off the coasts of Texas and Louisiana; and from various marine seafood from the Chesapeake Bay and the New England shore area.

In the largest outbreak in the United States to date, which occurred in Maryland in August 1971, 320 persons became ill eight to twenty-two hours after consuming steamed crabs. The median incubation period was 15 hours and the median duration of illness was two days. Symptoms included diarrhea (98 percent), abdominal cramps (78 percent), nausea (76 percent), vomiting (74 percent), fever (26 percent), headache (25 percent), and chills (10 percent). V. parahemolyticus was cultured from enteric specimens and seafood.

By considering symptoms and incubation periods, illness from V. parahemolyticus may be distinguished from that of staphylococcal poisoning, clostridium perfringens poisoning, and salmonella infection in *outbreak* situations. No great reliance as to probable cause, however, should be placed on reviewing the symptoms of a single case of food-borne illness. Table 1 summarizes the distinguishing features.

TABLE 1.—*Distinguishing Features of Vibrio Parahemolyticus*

Etiologic Agent	*Median Incubation Period (hours)*	*Fever*	*Vomiting*	*Diarrhea*
Staphylococcal enterotoxin	3	−	+	+
Clostridium perfringens	12	−	−	+
Vibrio parahemolyticus	15	±	+	+
Salmonella	24	+	+	+

V. parahemolyticus is undoubtedly unrecognized in some outbreaks from seafood in which salmonellosis or shigellosis is initially believed to be the etiologic agent but where these agents cannot be confirmed in the laboratory. V. parahemolyticus requires high salt and pH concentrations to suppress the growth of other organisms. Thiosulphate citrate bile salts agar (TCBS) is one of the recommended media for its isolation.

Although illness due to V. parahemolyticus has not yet been reported in California, physicians should be alert to this potential pathogen.

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Zoster Immune Globulin (ZIG)

In 1971 the Center for Disease Control in Atlanta established a program for the distribution and study of zoster immune globulin (ZIG) and release of the material began in January, 1972. This investigational material prepared from the plasma of healthy donors convalescing from herpes zoster was demonstrated to be a safe and effective agent in the prevention of severe varicella (chickenpox) in susceptible persons when given within 72 hours of exposure. It is indicated for patients with impaired or suppressed immune status (secondary

to malignancy or immunosuppressive medications) for whom varicella can be severe or fatal. Release of ZIG is arranged through designated regional consultants. In California the consultants are Dr. Paul Wehrle in Los Angeles and Dr. Moses Grossman in San Francisco. Administration of ZIG should be confined to patients who have no history of varicella and (when the test is available) a negative varicella-zoster (VZ) complement fixation test who are significantly immunosuppressed and who have been closely exposed within the preceding 72 hours to persons with either varicella or herpes zoster. Close exposure is defined as a prolonged intimate contact such as with a sibling or a playmate seen daily. The national supply of ZIG for this purpose is limited. Physicians and medical facilities are urged to refer patients in otherwise good health who are convalescing from herpes zoster to donate plasma for this program. Details regarding donor selection are available from the Vaccines Investigations and Evaluations Unit, Center for Disease Control, Atlanta, and from the California State Bureau of Communicable Disease Control in Berkeley (telephone number: (415) 843-7900, ext 249).

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Primary Amebic Meningoencephalitis

PRIMARY AMEBIC MENINGOENCEPHALITIS is a newly recognized lethal disease which appears to be potentially treatable.

Acanthamoeba are widely disseminated not only in soil, but also in water, sewage and other decaying matter. Both epidemiological and laboratory evidence suggest that these protozoa feed mainly on fecal bacteria, and that infection is usually associated with immersion in contaminated water warm enough to permit their propagation. Culbertson et al demonstrated in 1959 that acanthamoeba could produce meningoencephalitis if introduced either intracerebrally or by the nasal route in laboratory animals. In 1965 Fowler and Carter reported cases of acute pyogenic meningitis and since then at least 57 cases have been reported in the literature, although in only 15 of these cases were ameba present.

Most of the reported cases of amebic meningoencephalitis have occurred in warm climates, and usually there is a history of swimming. In one instance the patient had swum in a heated indoor pool, and in another in a hot mineral spring. In another instance, immersion in a mud puddle formed by a thunderstorm was indicated.

In 1970, Apley reported the use of amphotericin B in three children, only one of whom died. In a review article by Carter in 1972, additional success of amphotericin B treatment was reported.

Therefore, the diagnosis of primary amebic meningoencephalitis should be considered in all patients with purulent meningitis in whom no bacteria can be found on Gram-stained smear. In view of the lethal natural history of this disease, amphotericin B therapy should be started as soon as the diagnosis is established.

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Herpesvirus Infections and Cancer of the Cervix

HERPESVIRUS HOMINIS, TYPE 2, (HSV-G) has become recognized as a sexually-acquired infection in recent years. Further, an association between cervical cancer and sexual activity was noted by Terris. Inevitably, investigators turned their attention to a possible relationship between genital herpesvirus and cervical carcinoma.

Several workers in this field have reported similar findings which show an increased prevalence of HSV-G antibody in women with cervical neoplasia as compared with matched controls without evidence of dysplasia. Nahmias et al found women having HSV-G and dual antibodies (a mixture of Types 1 and 2) as follows: invasive carcinoma 83 percent, controls 35 percent; *in situ* cervical carcinoma 70 percent, controls 24 percent; histologically confirmed cysplasia 56 percent, controls 18 percent, cervical atypia diagnosed by cytological examination only 40 percent, controls 20 percent.

Royston and Aurelian, using a different technique, demonstrated a similar difference between study cases and their respective controls. However, their studies show the presence of antibodies in 100 percent of the cases of both invasive carcinoma and carcinoma *in situ* and in 92 percent

of those with atypia. Their work further demonstrates an increase with age in the prevalence of HSV-G antibody in women free of cervical neoplasia. Those between 15 and 24 years of age show a prevalence of 36 percent while those from 45 to 54 show 71 percent. Those 55 and older show no further increase in prevalence. In addition, their findings indicate an inverse relationship between the prevalence of antibody and social class.

While more investigation is needed to establish a causal relationship, it is apparent that women with a known genital herpesvirus infection should be closely watched for early signs of cervical neoplasia.

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Mumps Vaccine

MUMPS IS NOT as innocuous a disease as it is commonly considered and complications can occur in a significant number of cases. Orchitis occurs in about 20 percent of cases and although subsequent sterility is rare, it can develop as a consequence of severe cases. In addition, it has been estimated that 10 to 15 percent of all mumps cases demonstrate some evidence of meningoencephalitis which makes mumps the most frequently documented cause of viral central nervous system disorders. Notwithstanding the pain, discomfort and medical complications of mumps, its economic cost, which includes direct medical costs, loss of school days, and loss of work for some parents who have children ill with mumps, can easily justify the cost of prevention.

An effective, live, attenuated mumps vaccine was first licensed for public use in 1968. Initially, because of uncertainty as to how long immunity conferred by this vaccine might persist, its use was recommended only in children and adults over the age of ten who had no history of clinical mumps. However, with more experience and data concerning the persistence of vaccine-induced antibody, many now believe that children older than one year should not be denied the protection the vaccine affords. Sales of mumps vaccine in California since 1968 have only totaled about a million and a half doses. Efforts to encourage mumps immunization have been hampered by the following major factors: (1) the vaccine is expensive, (2) it is not included in the provisions of federal funding under the Immunization Assistance Project, and (3) mumps is not considered by physicians as a serious public health problem. With a combined trivalent vaccine (mumps, measles, rubella) now available, a start should be made to intensify immunization against mumps throughout the state.

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EDITORIAL

Useful Strategies in Dealing with Transfusion Therapy

IT IS ESTIMATED that more than eight million units of blood and blood products are used in this country each year. Judging from this volume of activity alone, it is inescapable that the clinical use of blood and blood products represents an important therapeutic modality.

Human blood constitutes a national resource since it meets the criterion of a resource whose availability is restricted, being dependent on the motivation and participation of a limited population of human donors. The efficient operation of a transfusion service which utilizes this blood resource involves a fine balance between the regional input or supply of blood and the output or clinical use of blood. The physician, who controls one side of this equation, has a dual responsibility when he orders and uses blood and blood products. His primary responsibility is to assure safe and effective therapy for his patient. But if he fails to meet this obligation, either because of unnecessary use of blood or the use of an inappropriate component, he may act to deplete the regional blood reserves and may, in effect, deny the availability of blood to some other patient. These are not idle theoretical speculations. In the face of current demand, the supply of blood can only be described as marginal, and we have witnessed repeated episodes of blood shortages in different areas of the country which have necessitated the cancellation of elective surgical procedures.

The interplay of social, moral and ethical problems associated with the procurement of blood may in some situations complicate the straightforward application of transfusion therapy to clinical medicine. To cite an example, it is now recognized that the buying and selling of blood has more tangible consequences than just the moral implications of such a practice. It has been repeatedly documented that blood from paid donors carries a significant risk of hepatitis for the recipient.

The physician should be aware of the three basic elements affecting the operation of a blood transfusion service, even though he may not always be in a position to affect all these elements. First, there is the large problem of obtaining blood, which involves the recruitment of sufficient donors to maintain a predictable and steady supply of blood to meet clinical needs. Obviously this is not the place to consider this aspect, although it is difficult to see how the physician can long remain unaware and unconcerned about the availability of blood. Second, there is the need to utilize the blood efficiently after it has been obtained from the donor. Appropriate responses to this need involve: the more efficient control of blood resources by regionalization of blood banks, efforts to manipulate blood inventories with the help of computer technology so as to minimize outdating and exercise control over blood input, and efforts to develop blood preservation techniques which will extend the shelf-life of blood and blood components. Finally, the physician directly impinges on the system through his use of blood. He has an obligation to keep current with developments in transfusion therapy so that he can utilize the safest and most effective blood component in treating his patient. Through the use of component therapy, the physician is able to achieve more effective therapeutic levels of the desired component, and to extend the available blood resources since each unit of whole blood can meet the needs of multiple recipients.

For reasons not entirely clear, blood banking and immunohematology have been neglected areas in clinical medicine. There is a need to attract and develop a specialized cadre of medical manpower

that will extend and promote high quality care in this area of clinical medicine. In part this deficiency may have been due to the impression in the past that the blood bank was essentially a "supermarket" type of operation serving solely as a repository for blood.

The review of current transfusion therapy by Hinkes and Steffen in this issue of CALIFORNIA MEDICINE clearly shows that we have come a long way from the era when blood was used to correct anemia and traumatic or surgical hemorrhage. Current transfusion therapy is a complex and sophisticated discipline that deserves the serious consideration of the clinician. Immunohematology and the clinical use of blood have expanded rapidly since World War II and have benefited from major advances in hematology, immunology, biochemistry, cardiology, genetics, and technology such as plastic bags and the refrigerated centrifuge. Hinkes and Steffen have tried to show that the clinician needs to be aware of the rapid advances in blood banking if he is to provide the safest and most effective transfusion therapy. The proper use of blood requires: a knowledge of the pathophysiology of the condition being treated, identification of the specific deficiency in the patient, and the choice of the appropriate product. Their review provides a useful discussion of the large number of products currently available for transfusion therapy, deals with some aspects of blood storage and summarizes the available information on transfusion-transmitted hepatitis which constitutes a major risk in transfusion therapy. Probably, because of space limitations, they do not discuss exchange transfusions used in pediatric practice for treatment of hemolytic disease of the newborn due to feto-maternal blood group incompatibility, nor do they discuss the use of blood in extracorporeal or cardiac-bypass shunts.[1] It should also be emphasized that hepatitis is not the only risk or hazard associated with the use of blood. Some of these reactions such as the immediate hemolytic transfusion reaction or the use of blood contaminated with cold growing Gram negative organisms can be as life-threatening as hepatitis.[2,3]

There are a number of topics in blood banking in which there is no unanimity of opinion at our current state of knowledge. One of these topics is the role of frozen blood in a transfusion service. Hinkes and Steffen have tried to present a balanced viewpoint and have enumerated the advantages and disadvantages of this product. The advantages of frozen blood enumerated by them have to be balanced against the current high cost of frozen blood. If the advantages of frozen blood were absolute and not attainable by other means, there would be no hesitation in promoting the adoption and use of frozen blood. But as Chaplin[4] has indicated, many of the advantages of frozen blood are relative and not absolute. For example, the very long shelf-life of frozen blood permits the stockpiling of blood so that a dependable supply can be kept on hand. Blood shortages, however, could also be avoided with liquid preservation of blood if efforts were directed to a more efficient use and control of donor recruitment, and by promoting the use of preservatives such as adenine which can extend the shelf-life of blood. Similarly the advantages of reduced hepatitis infectivity and the low incidence of immunization to HL-A antigens in potential organ transplant recipients, may be attainable with liquid stored blood by using more sophisticated epidemiological and laboratory detection techniques for hepatitis carriers and through the improvement of the techniques currently in use for preparation of buffy coat-poor blood. This is not to say that frozen blood is not an essential part of current transfusion therapy. Frozen blood has an established role in stockpiling rare blood types for later autologous or homologous transfusions. Overall, it does not appear to this reviewer that the across the board adoption of frozen blood programs in blood banks throughout the country is justifiable at this time.

On balance, Hinkes and Steffen should be commended for putting together an extremely useful review of transfusion therapy and for highlighting the large variety of problems that can be handled with the knowledgeable use of blood. It is to be hoped that physicians will take the time to familiarize themselves with this rapidly expanding field so that they can make available to their patients the best quality of care in this therapeutic modality.

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The Rise and Fall of Botulism

LIFE AND SECURITY in a world dominated by science and technology are possible only if history and the incontrovertible facts accumulated from experience are man's guides. An example of such admirable empiricism is the fine attention accorded to the diagnosis and public health aspects of botulism in the current issue of CALIFORNIA MEDICINE. This discussion is quite fitting in a journal published in this state, since in 1899 W. M. Lewis correctly identified the first case of botulism in California. His paper, describing "A Case of Ptomaine Poisoning" resulting from the consumption of a beef tamale was probably also the first such report in the entire United States. It appeared in the *Southern California Practitioner.*

Well over a thousand years ago, Emperor Leo VI (889-911 A.D.) of Byzantium managed to acquire the title "The Wise" because by edict he forbade the eating of blood-sausages as harmful to human health. He was able to act arbitrarily in restraining trade sans consultation with scientific advisors. After nine centuries, beginning in 1735 and particularly in 1793, public and professional concern was roused in Württemberg by classical outbreaks of blood-sausage poisoning. District Medical Officer C. A. J. Kerner deemed the disease reportable and collected details of some 230 cases over a period of 25 years. He attributed the disease to a toxic fatty acid developing within the sausage because of improper preservation by the smoking process used to "cure" the meat. The causative organism was isolated from inadequately cured ham in 1896. However, the prevailing belief that botulism was provoked mainly by ingesting sausages and only by foodstuffs containing animal protein was shaken by the occurrence of 11 fatal cases of typical botulism among 12 consumers of waxbean salad in Darmstadt in 1904. The episode attracted little attention until November 1913, when 12 young people attending a sorority party at Stanford University ate a salad containing string beans and mayonnaise. The string beans had been boiled for one hour on three successive days according to a method recommended in a U.S. Department of Agriculture pamphlet of the day. Dr. Ray Lyman Wilbur, who fortunately had observed some of the patients of the Darmstadt outbreak and was therefore prepared to recognize the malady, diagnosed the resultant disease as botulism. It was he who encouraged Ernest C. Dickson to conduct a thorough study of this poorly understood Clostridium poisoning. Dickson's studies revealed that sterilization of food by the cold-pack method usually employed by housewives in the Pacific States could not be accomplished if the raw vegetables had been contaminated with spores of C. botulinum, which are rather abundantly present in the dry surface soil at harvest season. Dickson was the first to observe that the spores of several suspensions could survive for two hours in boiling water. Hence he recommended that an educational campaign be instituted so that all who practiced the home-canning of fruits and vegetables might be informed of the danger of poisoning from the toxin of Bacillus botulinum. Little suspicion had yet accrued to commercial canning procedures. Then, with catastrophic rapidity, false security ended and grave responsibilities were thrust upon the canning industry in California. Between August and November 1919, in Canton (Ohio), Detroit (Michigan) and Java (Montana) ripe olives served at banquets caused a total of 28 intoxications with 17 deaths. Hence in December 1919 the Canners League of California, the California Olive Association and the National Canners Association proposed and liberally financed a detailed investigation by the G. W. Hooper Foundation of the University of California and the Department of Medicine, Stanford University. This project involved the dangers of botulism in commercially prepared food, how it originates, and how it could best be eliminated. A "botulism commission" was entrusted with the investigation. In the course of early studies, it became apparent that canned food liable to spoilage by botulinus organisms should be processed so that the sterility and sound appearance of the container at varying temperatures and altitudes, as well as proper handling, were ensured. Scientifically established sterilization stand-

ards replaced former procedures as the result of experiments exposing the spores of 107 different strains of C. botulinum (Types A and B) to five different heating temperatures and demonstrating that thermal destruction of the most resistant pathogens required a four-minute exposure at 248°F and 330 minutes at 212°F. The time and temperature essential for the destruction of the heat-resistant spores were calculated from the heat-penetration and thermal-time slopes. The commission recommended that olives and spinach be processed under pressure in retorts. The regulations merely coped with an emergency and hoped for the future application of scientifically established, guaranteed sterilization—without specifying the type and means of operating of equipment nor insisting on rigid, continuous inspection of the packing and processing procedures. Therefore understerilized, commercially packed food continued to cause botulism. Leaders of the California canning industry, realizing the benefits to be derived from a dependable, far-reaching, educational inspection service, voluntarily offered to finance Cannery Act 428. Approved in May 1925, it created a Division of Cannery Inspection in the State Department of Public Health to regulate the processing of low-acid foods and the sanitary standards of packing plants. All matters pertaining to processing times and canning procedures were carefully studied by members of the Laboratory for Research in the Canning Industries at the University of California, San Francisco. The laboratory is now located in Berkeley and financed by the California food packing industry and the National Canners Association.

California answered the public accusation of carelessness by instituting a system of control which restored complete popular confidence in the safety of its canned products. The information obtained by the California research was soon put into practice throughout the United States, and commercially canned food such as olives, spinach and string beans ceased to be a botulinogenic menace. In 1941, the presence of the toxin of a low-heat-resistant Type E C. botulinum in a commercial can of mushroom sauce could not be explained. It was not until 1963 that, incidental to other investigations, it was recognized that recontamination had occurred when the muddied cooling water taken from the city supply had seeped into the cans through faulty seams. Without delay, the California Inspection Service, in close cooperation with the National Canners Association, organized schools to train qualified inspectors to critically spot-check the closure or seams of containers and to supervise the methods employed in providing safe cooling water. The few cases of botulism, or the occasional discovery of botulin toxin in commercially canned food in the recent past, have been the result of technical errors, modifications and innovations in handling, or installation of new, untested filling equipment—all aimed at increasing production and reducing labor costs—but not a result of the process of sterilization per se.

Drying and smoking, as methods of food preservation, have justly received much adverse publicity, particularly in 1963, when catastrophic outbreaks of Type E botulism from smoked fish occurred in several states. Examination revealed that the raw fish were contaminated. Obviously, better sanitation practices and more rigidly controlled heating and smoking procedures are essential.

In response to public indignation, accusations and sensational publicity, a considerable amount of misinformation was disseminated in connection with the so-called "vichyssoise" episode of June 1971 in New York. The American canning industry, acting via the National Canners Association, requested a form of self-regulation under the surveillance of the Federal Food and Drug Administration. The regulations are now in the process of promulgation. They will bring to the people results of scientific research, technological advances, and the expertise of nearly 50 years of canning experience, all of which may help to reduce to the very minimum the serious consequences of botulin contamination—a hazardous toxicity maintained by the ubiquitous presence of six immunologically different C. botulinum spores in the environment of raw produce.

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Toward Greater Unity and Greater Strength

THE HOUSE OF DELEGATES meeting in March was privileged to hear timely and perceptive statements from two able and dedicated leaders of our profession. The statements of the outgoing and incoming presidents of the California Medical Association are reported elsewhere in this issue. They merit thoughtful attention.

An unusual and singularly impressive part of Dr. Crum's presentation unfortunately cannot be reproduced in these pages. It was a motion picture which dramatically symbolized the fragmentation which saps if indeed it will not destroy the strength of the medical profession. In the film a woodcutter with a chain saw systematically removes one sturdy limb after another from what had obviously once been a strong and noble tree, to the accompaniment of loud and sometimes raucous cries of "Right," "Right," "Right" from physicians frustrated by what is occurring in medical care. All that finally remained was a stump with a few very severely pruned limbs. The viability of this once mighty tree was obviously greatly impaired if not totally lost.

The message was clear. The medical profession has been and is being cut to pieces, often to the acclaim of well-meaning physicians and others who disagree with what is going on and what is being done about it, and unless all or much of it can be gotten back together again, a once mighty profession will surely lose more of its strength and perhaps even its viability as an independent entity.

The fragmentation which has occurred needs little documentation. The proliferation of medical science has given rise to a myriad of scientific specialty societies which serve specialized interests and often claim the major professional allegiance of their members. Specialization has also grown among organizations within the health care delivery system with the appearance of powerful organizational advocates of public health, group practice, private practice, hospitals, medical schools and many other essential segments of what should be a more coordinated rather than a more fragmented health care system. And at the ideological level physicians and others who seek to maintain and preserve a system of medical practice which they know to have worked well for them and their patients, find themselves resisting and sometimes resenting a growing criticism of this traditional practice and a growing advocacy of a different sense of social, economic and political responsibility and commitment in medical and health care. All these divisions, scientific, organizational and ideological, have brought about a substantial lessening of the traditional strength and viability of the medical profession, and of the efficiency and effectiveness of medical care as a whole.

Fortunately there are signs that some reversal has begun. Once again the California Medical Association appears to be in the lead. More than ten years ago it began by creating the Scientific Board to strengthen the ties between the CMA and the scientific specialty societies. Later when the Advisory Panels became part of the Scientific Board structure these ties were greatly strengthened and new important links were established in each specialty with each of California's eight medical schools. The Scientific Board has become an effective instrument to coordinate medical science in California and to bring it more effectively to bear upon problems of medical practice and medical care in this state. Representatives of the Scientific Board now sit as members of the House of Delegates but it yet remains for them to be given the right to vote. When this occurs an enormously important symbolic step will have been taken. The CMA will have reincorporated specialized medical science not only into its deliberations but into its decision-making process as well.

The approach to incorporating other organizations representing other facets of the health care delivery system into the deliberations and decision-making processes of CMA is far less developed. But a start has been made. For some years now CMA has made an increasing commitment of time, energy and substance to bring about a better exchange of information and where possible to collaborate with other organizations and agencies

to improve one or another aspect of medical or health care. The emphasis has been on collaboration and cooperation where there are areas of common interest and on the resolution of disagreements where this is possible. The net result has been significant progress toward greater unity and more coordination of effort. It is probable that as much has been accomplished here in California as anywhere in the nation, but there remains much more to be done.

Progress in overcoming barriers and misunderstanding between older and younger physicians has been rapid and truly rewarding to all. For several years there has been increasing involvement of CMA with young physicians (interns and residents) and physicians-to-be (medical students), and vice versa. All have come to the realization that physicians, young physicians and physicians-to-be must work as closely and effectively together as possible if the common goal of better medicine and better health care for all is to be achieved. At its recent meeting this was recognized by the House of Delegates which took the enormously significant, and in a sense symbolic, step of giving voting representation in the House to representatives of these young physicians and physicians-to-be.

Yes, there is impressive evidence that important steps are being taken to get it all back together. These are welcome steps toward the greater unity and greater strength which are needed if a great profession is to remain a viable and sturdy independent entity. The leadership of the California Medical Association is to be commended and supported. It is not to be forgotten that the same forces which produced greater specialization and fragmentation also, and in similar meaasure, produce greater interdependence among the specialized and fragmented segments of medical science and medical care. It is the interdependence which now needs the more particular attention from organized medicine and others concerned with health care. In California, at least, it is beginning to get this attention.

—MSMW

CASE REPORTS

Refer to: Devor D, Bandell H: Kidney autotransplantation for ureteral loss from granulomatous colitis. Calif Med 118:67-68, May 1973

Kidney Autotransplantation for Ureteral Loss from Granulomatous Colitis

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KIDNEY AUTOTRANSPLANTATION has been used in the past for management of a damaged and inadequate ureter but it has not previously been reported as a successful procedure for correction of injury due to intestinal fistulization associated with complications of granulomatous colitis.

Report of a Case

The patient was a 29-year-old white truck driver who was diagnosed as having ulcerative colitis in 1963. Bloody mucoid stools led to admittance and treatment in a military hospital. Prednisone, Azulfidine® (salicylazosulfapyridine) and diet therapy resulted in remission of symptoms until he began to have abdominal cramps and 10 to 15 loose stools a day, with blood and mucous admixture. In 1969 he was admitted to hospital after outpatient therapy with prednisone failed to evoke remission. Inpatient care with prednisone, Azulfidine and diet therapy again produced a remission.

Left flank pain and fever required admission to hospital in July 1971. A barium enema roentgenogram demonstrated a fistula between the descending colon and the left flank muscles. On laparotomy the active disease was found to be confined to the descending colon and the associated fistula. The diagnosis was corrected to granulomatous colitis. The descending colon was excised and the transverse colon was joined to the rectosigmoid. A left flank abscess was drained in the postoperative period and the wound closed uneventfully. An excretory urogram (IVP) performed at this time demonstrated a normal upper urinary tract (Figure 1).

In September 1971, hematuria developed and, on the basis of the clinical course and excretory urography, a left ureteral calculus was diagnosed. Symptoms and physical findings reverted to normal on conservative management.

Recurrent left flank pain prompted readmission in December 1971. A midureteral obstruction was identified radiographically (Figure 2). At exploration, the midportion of the ureter was found to be encased in fibrous inflammatory tissue. The ureter itself was stenotic and nearly destroyed by inflammatory changes. A 4 cm segment of ureter was resected and end-to-end ureteroureterostomy was performed. The margins of the ureter were not free of inflammatory changes, which decreased the chances of successful healing. The anastomosis site was splinted with a No. 8 French indwelling polyethylene catheter. On the fourteenth postoperative day, the catheter was removed and within two days a ureterocutaneous fistula became manifest. A repeat IVP showed midureteral obstruction (Figure 2).

An arteriogram performed by the transfemoral Seldinger technique demonstrated normal renal function and parenchyma bilaterally, as well as a solitary renal artery on the affected side. The patient was readmitted in January 1972 for definitive treatment. The left kidney was autotransplanted to the right iliac fossa. Ureteroneocystostomy was performed. The patient had an uneventful post-

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Figure 1.—Excretory urogram in 1969 showed no abnormality of upper urinary tract.

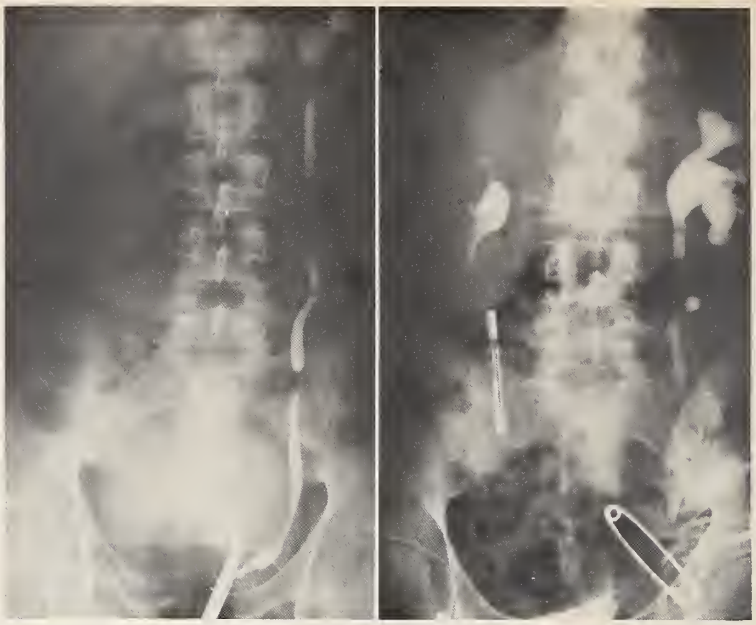


Figure 2.—Left, a midureteral obstruction was demonstrated radiographically in 1971. **Right,** fourteen days after resection of a segment of ureter and end-to-end ureteroureterostomy, an excretory urogram showed midureteral obstruction.

operative course and was discharged on the twelfth postoperative day. An excretory urogram on the tenth postoperative day demonstrated normal function of the autotransplanted kidney and the ureteroneocystostomy.

Discussion

Granulomatous colitis produces a variety of urologic problems as a result of fistulization, inflammation, dehydration and metabolic disturbances. Ureteric obstruction and destruction, calculus disease, enteroureteric and enterovesical fistula are well recognized hazards in these circumstances.[1]

In the present case, when primary reanastomosis of a partially destroyed ureter failed, a variety of alternatives was considered. The possibilities were: (1) mobilization of the kidney and ipsilateral reanastomosis, (2) ureteral mobilization with ureteroureterotomy, contralaterally, (3) nephrectomy, (4) use of an ileal segment to bridge the ureteral gap. The first and second alternatives were rejected because of the ligneous changes in the retroperitoneal tissues and compromised ureteral length. The third and fourth alternatives were rejected because of the active intestinal tract disease and inflammatory changes within the peritoneum. Nephrectomy and kidney autotransplantation were the only acceptable alternatives.

Autotransplantation is an attractive procedure because it offers opportunity to preserve the urinary system and does not entail immunologic complications. The procedure has been made feasible by the numerous technical advances incidental to the development of homotransplantation. It has been used for renal artery stenosis,[2] for fibromuscular hyperplasia,[3] and for iatrogenic ureteral loss,[4] but not previously for granulomatous colitis.

In the present case the patient's course was classical for granulomatous colitis in that it was prolonged and was fraught with both intestinal and urologic complications. In the circumstances an unusual effort to preserve the urinary system intact appears particularly worthwhile.

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Refer to: Rabens SF, Bauer M: Minimal scleroderma with extensive calcinosis cutis. Calif Med 118:69-71, May 1973

Minimal Scleroderma with Extensive Calcinosis Cutis

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DEPOSITION OF CUTANEOUS CALCIFICATION occurring during the course of the so-called collagen disease was reported as early as 1878 by Weber[1] and in 1911 by Thibierge and Weissenbach.[2] Scleroderma and dermatomyositis have been the two diseases most frequently linked with calcinosis cutis. Association with lupus erythematosus has been described as well, although much more rarely.[3,4] Calcinosis cutis in collagen disease increases in incidence with the duration of disease and with the severity of cutaneous involvement. It is unusual for extensive calcification to occur early in scleroderma when clinical evidence of collagen damage is minimal.

Report of a Case

The patient, a 49-year-old black woman, first noticed hard nodules on all extremities and on the buttocks in 1968. Two years later, she was admitted to hospital because of congestive heart failure with atrial flutter and a 2:1 block. A carbon dioxide study demonstrated a pericardial effusion. Physical examination revealed numerous subcutaneous and peri-articular nodules. X-ray examination showed dense soft tissue opacities consistent with calcification (Figures 1, 2 and 3). There was an abscess on the right elbow. Cardiac symptoms were relieved by cardioversion and administration of digoxin, quinidine and diuretics.

In the following year, several ulcerations appeared about areas of calcification on the fingertips (Figure 4). Although the patient's hands felt cold, they were never painful. No sclerodactyly or telangiectasia was present, and there was good capillary filling in all digits. A sinus tract persisted near the right elbow. From it the patient could easily express a chalky, white liquid containing calcium as determined by chemical analysis (Figure 5).

Another abscess appeared on the left knee and the patient was again admitted to hospital in November 1971. Physical examination, at this time, revealed a few firm hypopigmented patches with pigmented follicular macules in both inguinal areas, on the forehead, and on the back of the neck (Figure 6). There was some recession of the hairline. The skin on the forearms was taut, but could be lifted. The facial skin was smooth with little wrinkling. There was no restricted motion of the face or mouth, and the facial skin was easily pinched. All hand and finger movements were intact.

Hemoglobin was 12.4 grams per 100 ml. Leukocytes numbered 11,400 per cu mm with a normal differential. Platelets were normal. Urinalysis showed no albuminuria, glycosuria, casts, or red

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Submitted July 6, 1972.

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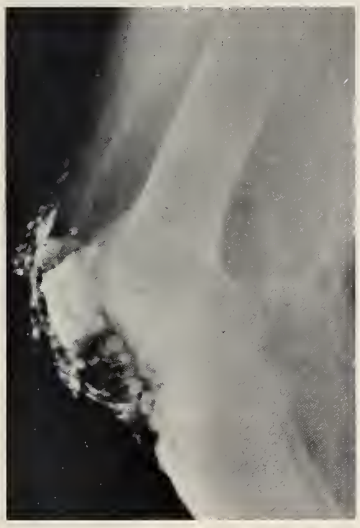


Figure 1.—Soft tissue calcifications about left knee.

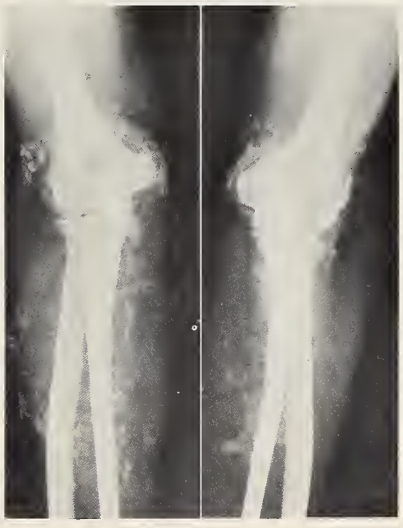


Figure 2.—Extensive calcification in both upper extremities.



Figure 3.—Normal joint spaces and soft tissue calcification.

blood cells. The blood sedimentation rate was 15 mm per hour. Electrolytes and blood sugar were normal. Albumin content was 3.4 grams per 100 ml, with globulin 4.8 grams. Serum protein electrophoresis was within normal limits aside from a slight elevation of alpha-2 globulin. Bilirubin, protein-bound iodine, T-3 uptake, uric acid, cholesterol, aldolase, creatine phosphokinase, and serum glutamic oxalic transaminase were all normal. Serum calcium was 10.3 to 10.6 mg per 100 ml and serum phosphate was 3.7 to 4.0 mg per 100 ml on three determinations. Twenty-four-hour urine calcium was 0.6 mEq, 1.6 mEq, and 5.9 mEq on three occasions (2.5 to 20 mEq normal); and 24-hour urine phosphate was 0.19 mEq (up to 3.5 mEq normal). Alkaline phosphatase was 2.5 units (1 to 3 units normal). The VDRL test was nonreactive. Rheumatoid factor, cryoglobulins, antinuclear antibody tests, and lupus erythematosus preparations were negative in three determinations. Serum complement was 960 units. Culture of the abscess on the knee revealed Klebsiella aerobacter and Staphylococcus aureus coagulase positive. Upper gastrointestinal tract and barium swallow roentgen studies were normal. On chest and abdominal films, very slight cardiac enlargement and minimal calcification in the abdominal aorta were noted. An intravenous pyelogram showed no renal calcification or other abnormality. Studies of bones and of the hands showed much soft tissue calcification with no bone resorption and normal joint spaces.

On histopathologic studies of skin from areas of calcification, thickening of the dermis was noted, with dermal deposits which stained black with a von Kossa stain for calcium. The collagen bundles were large and closely packed, with a reduction of the interfibrous spaces. The fat around eccrine sweat glands as well as the subcutaneous fat appeared to be replaced almost entirely by connective tissue. Sebaceous glands and hair follicles were sparse. The epidermis appeared normal, and there was no inflammatory infiltrate (Figure 7). These findings were consistent with the histopathological changes in scleroderma recently described by Fleischmajer et al.[5]

Discussion

Calcification seen in the collagen diseases is termed dystrophic calcification and the deposits are a local response to tissue injury. The serum calcium and phosphorus are normal, and no evi-



Figure 4.—Finger and finger tip calcifications.



Figure 5.—Sinus tract, right elbow. Note chalky, white material containing calcium expressed from this area, with many deposits.

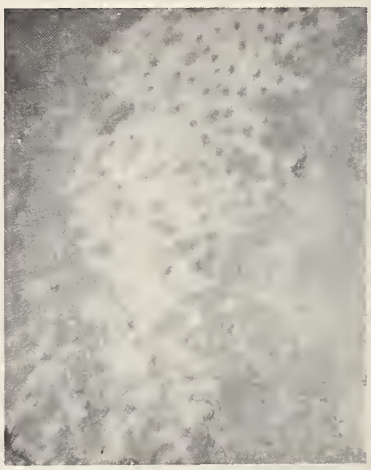


Figure 6.—Inguinal area. Hypopigmented firm patch with pigmented follicular macules.

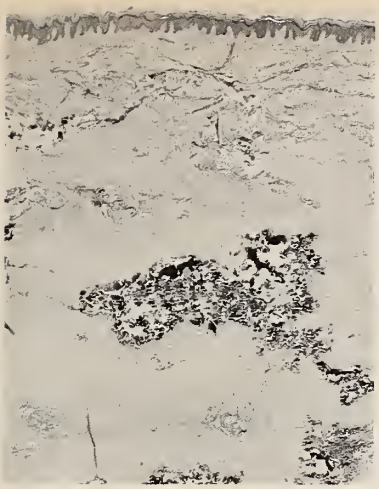


Figure 7.— Forearm. Note thick dermis with closely packed collagen bundles, sweat glands trapped by collagen, dermal calcifications, and absence of hair follicles, sebaceous glands, and subcutaneous fat. (Hemotoxylin and eosin, X 50)

dence of a systemic abnormality of calcium or phosphorus metabolism, such as occurs in hyperparathyroidism, is seen. *Calcinosis universalis* is a term sometimes reserved for calcium deposition in the dermis, subcutaneous tissue, or muscles without any known predisposing local tissue damage or systemic metabolic disorder.[6,7]

In all cases, when nodules or plaques are deposited, the surrounding tissue may become erythematous, infected, tender and painful, with ulceration of overyling skin and discharge of a chalky material containing predominantly calcium phosphate with some calcium carbonate.

Dystrophic calcifications are usually confined to areas of local connective tissue or lipid damage. There are several explanations for this event, some of which are based on animal experiments. Destruction and lysis of fat cells results in cellular debris which may combine with calcium ions to produce calcium soaps in affected areas.

In addition, tissue injury releases alkaline phosphatase, which initiates the calcification process. The explanation for this phenomenon is based upon the interaction betwen alkaline phosphatase and polyphosphates. Polyphosphates have been shown to inhibit the precipitation of calcium phosphate. The alkaline phosphatase released inactivates the polyphosphate compounds, thereby allowing calcification to occur.

Calcification is thought to occur in areas of altered collagen and ground substance. The nature of this change which facilitates calcium deposition in these tissues is under investigation.[5,8-11]

Calcinosis cutis is seen in dermatomyositis an average of two or three years after the onset of the disease. Usually this development is concomitant with other findings, particularly muscle weakness and enzyme elevation. In scleroderma, extensive calcinosis cutis is a rare sequela. It occurs most frequently with severe acrosclerosis and is usually a late complication—on an average, 11 years after onset of the disease. It is more frequent in women, and is said to offer a more favorable prognosis because it is a sign of long-standing disease.[12-17]

The patient in the present case is of interest because she has extensive calcinosis cutis without acrosclerosis or many other signs of scleroderma. Calcinosis cutis was diagnosed before scleroderma, thus reversing the usual sequence. The only manifestation of internal disease in this case has been one episode of congestive heart failure, arrhythmia and pericardial effusion.

The lack of clinical and laboratory evidence of systemic lupus erythematosus and dermatomyositis, the appearance of the few firm, hypopigmented areas with pigmented follicular macules, the taut skin of the forearm, the cardiac manifestations, and several confirmatory biopsies suggest scleroderma as the most probable explanation for the extensive calcification.

Summary

Calcinosis cutis complicating scleroderma usually occurs as a secondary event following extensive disease of many months' duration. The case reported is noteworthy because the extent of the calcinosis cutis seems disproportionate to the minimal amount of demonstrable scleroderma.

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Refer to: Anderson CE: Pilot study of Medicare patients' experiences and attitudes (Government and Medicine). Calif Med 118:72-76, May 1973

A Pilot Study of Medicare Patients' Experiences and Attitudes

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There has been widespread interest in the effect the Medicare law has had on the level of physicians' charges. This subject and other aspects of the present Medicare method of physician reimbursement is currently under study by Congress and the Department of Health, Education and Welfare. A group of Medicare patients recently seen and treated by the author were queried as to their experiences in paying for physicians' services under Medicare. A 64 percent response rate and the substance of the replies to a questionnaire suggests that this is a feasible mechanism for eliciting the attitudes and problems in a group of patients in the Medicare program.

A study is now being carried out by the Health Insurance Benefits Advisory Council in order to determine what effect the present mechanism of physician reimbursement under Medicare Part B has upon the level of physicians' charges generally, what factors influence assignment or non-assignment of benefits, and what problems the present reimbursement mechanism poses for beneficiaries. Inquiry also is being made into what alternative mechanisms might be useful. The purpose of the study is to make recommendations which might improve the reimbursement system under Part B of Medicare.

Members of the study team felt that it would be valuable to have an expression of opinion from patients who have had to rely upon Medicare for assistance in meeting the costs of illness or injury during a recent period. I have been of the opinion that the physician who actually treated such patients would be in an excellent position to inquire of his own patients as to their problems, attitudes and recommendations resulting from their experiences in utilizing physicians' services under Medicare.

To test this hypothesis, I devised a questionnaire and mailed it in March, 1972, with a covering letter to each of the 59 patients—40 women, 19 men—I had seen for the first time as new Medicare patients during the year 1971.* As my

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*The study was conducted at no cost to any governmental agency.

practice consists entirely of orthopedic surgery, most of the patients had problems relating to the musculoskeletal system. The range in age was from 65 to 93 years, the median age 71.8 years. The median age of the female group was very slightly above that of the male group. All responses were unsigned and no attempt was made to identify any respondent.

Of the 59 questionnaires mailed, 38 were returned—a response rate of approximately 64 percent. One of these replies was eliminated from the analysis because the patient was a former federal employee and had benefits under the Federal Employees' Program. As it is known that some of the patients to whom questionnaires were sent are dead and others are in states of severe senile debility, the response rate of more than 60 percent is considered excellent. The 37 valid responses were analyzed and constitute the basis for this report.

The Questionnaire

The questionnaire (Appendix A) was in four parts:

Part A—"The Medical Care Experience" was designed to determine the patients' recollection of the reason they sought medical care, the degree of satisfaction with the care received, impressions about the level of the physician's charges and impressions as to how rapidly physicians' charges in general have changed during the past five years.

Part B—"Paying the Bill for the 1971 Illness or Injury" was designed to find out just how the patient was billed, patients' preference with regard to direct billing or assignment, the proportion of the doctor's bill which was paid by Medicare and the presence and type of additional insurance to assist in paying the bill.

Part C—"About Medicare." Four true and false questions were designed to determine whether or not the patient felt that Medicare had been very helpful to him in his illness, the degree of burden that the monthly premium for Part B involves for the individual, and the patients' attitudes about payment for prescription drugs by Medicare.

Final Question—The final question was designed to determine what aspect of the Medicare Part B program caused the greatest trouble to the respondents.

A further space was added for "comments" on subjects which the patient felt needed elaboration or subjects not entirely covered by the questionnaire.

Validity of Responses

In the design of the questionnaire, several "tests" were incorporated: The first question, asking "What was your medical problem requiring the doctor's care?" tests the patient's recall of the reason he went to the doctor, thus giving some indication as to the patient's memory and clarity of recollection. Thirty-four of the 35 respondents answered this question in a straightforward and lucid manner. Only one respondent left the space blank.

Question No. 2, relating to the degree of satisfaction with the care received, was included to determine possible bias which might have a bearing on the other responses. For example, the patient who indicated he was "well satisfied" with the care received would probably be less inclined to feel that the charges made by the physician were excessive than would a patient who was "disappointed" with the treatment.

Questions Nos. 9 and 10, relating to the degree of help provided by Medicare, were arranged in such a way that a "true" answer to question 9 would almost certainly require a "false" answer to question 10. The failure of a respondent to answer question 10 correctly following his response to question 9 would demonstrate inconsistency and unreliability. Twenty-eight respondents answered "true" to question 9 indicating that Medicare was of great help to the respondent during his illness or injury, and 29 answered "false" to question 10, indicating that Medicare may be of great help to some people, but not very much to the respondent. One respondent who answered "true" to question 10 and did not answer question 9, indicated that his non-response to question 9 was due to the fact that his medical care expenses during 1971 were "very low" and did not exceed the deductible level. Only one respondent answered "true" to both questions 9 and 10, indicating some confusion or lack of understanding.

The impression gained from these tests is that those who responded were quite alert and reliable in their responses and evidently were mentally competent.

Results

Question No. 1. Of the 37 respondents, 35 answered this question. The answers were divided into three general categories: trauma, degenerative, and metabolic. Seventeen respondents indicated that they sought medical care because of

fracture or other traumatic complaint. Seventeen indicated a degenerative or attritional disorder, and one a metabolic problem (osteoporosis).

Question No. 2. Of 36 who responded, 32 indicated they were well satisfied with the care received, three were barely satisfied, one was disappointed.

Question No. 3. All 37 respondents answered this question about the doctor's charges:

- None felt that the charges made had been "much too high."
- Sixteen felt that the charges were "somewhat high." Assignment of benefits had been accepted for two of these patients.
- Eighteen, including four who were "assigned," indicated the charges were "about right."
- Three responded that the charges were "less than expected."

Question No. 4. To the question concerning the rate of increase of doctors' charges during the past five years, there were 32 replies:

- None indicated that they felt charges had risen at least 100 percent.
- Twenty-seven indicated the charges had risen "some, but not nearly 100 percent."
- Five indicated that charges had risen "very slightly" during the past five years.

PART B—Paying the Medical Bill

To Question No. 5—acceptance or non-acceptance of assignment—all respondents replied:

- Thirty-one indicated that the physician had billed the patient directly. Six indicated that an assignment had been accepted. (This was a test of "recall." Assignment of benefits was accepted when requested by the patient.)

To Question No. 6—Preference regarding assignment of benefit—there were 33 replies:

- Ten of the 31 patients who had been billed directly indicated that they would have preferred the physician to accept an assignment.
- 18 patients indicated that they preferred to be billed directly.
- Five indicated no preference between assignment and direct billing.

To Question No. 7—The proportion of the physician's bill paid by Medicare—35 answered:

- Twenty-seven indicated that about 80 percent of the doctor's charges were paid by Medicare.
- Seven indicated about 50 percent.
- One, who indicated that he had not reached his deductible, indicated that there had been no payment by Medicare.

To Question No. 8—Additional insurance coverage for physicians' services—there were 36 answers:

- Fifteen indicated no additional insurance.
- Twenty-one indicated additional insurance, broken down as follows:

Medicare Title 19 (Medi-Cal)	1
Blue Cross	6
Blue Shield	7
Other insurance	9
Patients who had more than one type of additional insurance	2

There appeared to be no correlation between additional insurance and attitudes toward the level of charges (question No. 3).

PART C

Question No. 9—Twenty-eight respondents indicated that Medicare was of great help to them in paying for their illness or injury. Two indicated that it was not.

Question No. 10—Three indicated that Medicare may be of great help to some people but did very little for the respondent. Twenty-nine answered "false" to this question.

Question No. 11—Of 34 answers, six indicated the patient had had a difficult time in paying the $5.60 monthly premium for Part B. Twenty-eight patients indicated they did *not* have serious difficulty in paying the monthly premium.

Question No. 12—Twenty-eight respondents indicated that Medicare should pay most of the cost of prescription drugs. Four answered this question in the negative.

FINAL QUESTION

Only 24 respondents answered this question relating to the most troublesome aspect of Medicare Part B.

- Four patients indicated on the margin of the questionnaire that they did not feel that any part of the "Medicare Doctors Insurance" was troublesome.
- Of the 24 who did respond, nine cited "slow payment by the carriers."
- Six indicated "unreasonable charges by doctors."
- Four indicated the monthly premium for Part B coverage, and three each cited the deductible and the 20 percent co-insurance as being the most troublesome part of the program.

COMMENTS

Fifteen respondents wrote in additional comments. These are summarized below:

- Four respondents replied that they had no complaints about doctors or Medicare, indicating that they felt the prices charged were fair and that Medicare "did its share" in paying for services.
- Three patients indicated that Medicare should pay for prescribed out-patient physicial therapy.
- Two indicated that the real problem was not physicians' charges but the "high-level of hospital charges."
- Two respondents were highly critical of the Part B carrier, indicating failure to acknowledge receipt of claims and failure to answer letters of inquiry directed to the carrier.
- The following comments were offered in each instance by one respondent.

When several doctors are involved, the bills of all physicians should appear on one statement.

Medicare should pay part of the drug costs.

Doctors should always accept an assignment.

Doctors charge too much and don't do any good.

Discussion

This pilot study indicates that, in at least this limited universe, it is quite feasible to obtain significant responses in a study of this kind through direct inquiry from a physician to patients whom he has treated.

In a cohort as small as that encompassed in this inquiry a 64 percent response rate (with all responses judged to be valid on the basis of tests incorporated in the questionnaire) indicates that this is, indeed, a feasible method of eliciting patients' opinions and identifying their medical economic problems and expectations.

Although the sample is very small and cannot be said to reflect the attitudes of the entire Medicare patient population, on some of the questions there was an overwhelming predominance of attitude which may be interpreted to suggest the general attitude of the Medicare beneficiaries. These attitudes listed below appear to be significant:

- Medicare should pay most of the cost of prescription drugs (27 yes, 3 no).
- Medicare was of great help to me during my illness or injury (27 yes, 2 no).
- I do not have a very hard time paying the $5.60 monthly premium for Part B (27 yes, 6 no).

Other observations from this questionnaire indicate that there is no great preference as to whether the physician accepts an assignment or bills the patient directly.

The majority of patients in this study had insurance coverage supplemental to Medicare.

The most frequently cited problem with the Medicare payment mechanism was slow payment by the carriers.

APPENDIX A

Medicare Questionnaire

The questions are designed to obtain your reactions, opinions and recollections of problems which you may have had in paying for your medical bills during 1971. Please be as frank as possible. If you cannot answer a question, please leave it blank. Thank you.

PART A—THE MEDICAL CARE EXPERIENCE

Q. (1) *What was your medical problem requiring the doctor's care?*

Ans: _____

Q. (2) *Were you satisfied with the care you received?*

Ans: Well satisfied ☐
Barely satisfied ☐ *Check One*
Disappointed ☐

Q. (3) *What about the doctor's charges?*

Ans: Much too high ☐
Somewhat high ☐ *Check One*
About right ☐
Less than expected ☐

Q. (4) Based upon your own experience only, how much do you feel doctors' charges have risen during the past five years?

Ans: At least 100% ☐
Some, but not nearly 100% ☐
Very slightly ☐ *Check One*
Not at all ☐

PART B—PAYING THE BILL FOR YOUR 1971 ILLNESS OR INJURY

Q. (5) *Did the doctor bill you directly for his entire bill?*

Ans: Yes ☐
No ☐ *Check One*
Don't know ☐

Q. (6) *If your answer was yes to question 5, would you have preferred that the doctor bill the*

Medicare carrier and charged you only for the balance? (Assignment)

Ans: Yes ☐
No—I prefer to be billed directly ☐ *Check One*
Indifferent ☐

Q. (7) *Excluding drugs, what is your recollection or impression of the part of your total doctor's bill paid by Medicare?*

Ans: About 80% ☐
About 50% ☐ *Check One*
Much less than 50% ☐
None ☐

Q. (8) *Did you have coverage other than Medicare which paid some of the bill not paid by Medicare?*

Ans: No ☐
Yes ☐

If *yes,* was it:
Medi-Cal ☐
Blue Cross ☐
Blue Shield ☐
Other Insurance ☐

PART C—ABOUT MEDICARE

PLEASE answer the following True and False—(cross out F, if true; cross out T, if false.)

Q. (9) Medicare was of great help to me during my illness (injury) in 1971. (T) (F)

Q. (10) Medicare may be of great help to some people, but did very little for me. (T) (F)

Q. (11) I have a very hard time paying the $5.60 monthly premium for Part B (doctor services. (T) (F)

Q. (12) Medicare should pay most of the cost of prescription drugs. (T) (F)

FINAL QUESTION: Please check just one:

I consider the most troublesome part of Medicare doctors insurance:

The $50 yearly deductible ☐
The 20% of doctor's bills never paid by Medicare ☐
Unreasonable charges by doctors ☐
The $5.60 per month out of my Social Security check ☐
Slow payment by the carriers ☐

COMMENTS: Please write any additional comments or suggestions.

Thank you for your cooperation.

New CMA Officers and Representatives

*Dr. Thomas Elmendorf of Willows was installed as President of the California Medical Association at the annual meeting of the House of Delegates in Anaheim, March 10 to 14, and Dr. Stanley A. Moore, San Diego, was elected President-**Elect.***



DR. ELMENDORF



DR. MOORE

Results of other elections at the annual meeting were:

CALIFORNIA MEDICAL ASSOCIATION

Speaker of the House JOSEPH F. BOYLE, *Los Angeles*
Vice speaker of the House HENRY V. EASTMAN, *Tustin*
Council chairman E. KASH ROSE, *Napa*
Council vice chairman FREDERICK W. ACKERMAN, *Pleasant Hill*
New councilors (three-year term)
GLADDEN V. ELLIOTT, *San Diego* District 1, Office 1
JACK McCLEARY, *Sherman Oaks* District 4, Office 6
CHARLES HAIR, *Saticoy* District 5
Councilors (reelected for three years)
RALPH M. MILLIKEN, *Los Angeles* District 4, Office 3
FRANK A. ROGERS, *Whittier* District 4, Office 9
DAN W. CLARK, *San Jose* District 7, Office 1
SANFORD E. FELDMAN, *San Francisco* District 8, Office 2
FREDERICK W. ACKERMAN, *Pleasant Hill* District 9, Office 2
E. KASH ROSE, *Napa* District 10
C. JOHN TUPPER, *Davis* *Scientific Board Representative*

AMA DELEGATION

THOMAS ELMENDORF, *Willows* Alternate-at-large

BLUE SHIELD OF CALIFORNIA'S BOARD OF TRUSTEES

Trustees elected by CMA's House of Delegates
EDGAR G. LaVEQUE, *Los Gatos* (reelected)
MR. JAMES B. BOOE, *San Francisco* (reelected)
MR. DANIEL K. CHINLUND, *San Francisco* (reelected)
ROBERT ROWLAND, *San Diego* (new member)
MR. KIKUO NAKAHARA, *Oakland* (new member)
MR. RICHARD W. GONZALEZ, *Los Angeles* (new member)

MEDICAL EXECUTIVES CONFERENCE

Chairman: MR. DON W. SOWER, *Marin Medical Society*
Vice chairman: MR. R. G. BOWMAN, *San Diego County Medical Society*

Refer to: Elmendorf T: Personal care: A key to the future. Calif Med 118:78-80, May 1973

Personal Care

A Key to the Future

THOMAS ELMENDORF, MD, *Willows*
President, California Medical Association

WHAT IS THE REASON for our existence as an organization, the California Medical Association? Are we oriented primarily toward the public interest? Or are we oriented primarily toward professional interests?

Our constitution identifies our purposes as "to promote the science and art of medicine, to protect the public health and to better the medical profession." Clearly, such a dedication would lie in the public interest. But is that merely lip service, or do we "put our money where our mouth is"? If one looks at our budget as it is analyzed per program, it can be factually demonstrated that from two-thirds to three-fourths of our money is spent in the public interest. To be sure, there is overlapping of both professional and public interest. It might even be said that to be dedicated to the public interest would, indeed, be a dedication to our own professional interests. However, it is clear in my mind that the reasons for our existence are primarily related to the interests of the public.

It will be my objective during the next year to continue to make visible and to accelerate the visibility of CMA's positive programs related to to the public interest. As an organization, CMA need not take second place to anyone in its dedication to high quality, personalized, scientific medical care. For those of you who believe as I do, I throw forth the challenge to join with the association in a continuation of its purpose. For those of you who are concerned only with working conditions and wages, I suggest that you broaden your outlook. In the former instance, it is my belief that we can gather considerable public support for our positions; in the latter instance, I would hardly expect public support for such a primarily self-interest organization.

Concerns of the Public

What is the public interest? What is it that the public really desires? It would seem clear that when accident or sickness occurs each person

Address of the President: Presented at the Annual Meeting of the House of Delegates, California Medical Association, Anaheim, March 13, 1973.

Reprint requests to: Mr. David Greer, Division of Professional and Public Relations, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

individually wants for himself or his family the highest quality of medical care. "Forget the expense!" I would emphasize that the demand is not only for the best, it is often directed toward the highly technological or highly scientific: "Fly me to Mayo's!" or "Call in a specialist!"

On the other hand, the public in general is more concerned about the increasing costs of medical care than they are the quality. Feeling the pressures, the federal Congress enacted the Medicare and Medicaid programs, which really created the alleged "health care crisis" by implementing a demand which was already far in excess of the supply elements needed to satisfy it. The "crisis" was primarily a crisis in availability of or accessibility to medical care.

It is time for the profession to stand up and make visible to the public that for the most part quality medical care is expensive. In some instances costs cannot be reduced. Coronary and intensive-care units are expensive. But more important than that, with all our scientific advances in knowledge and technology, we must make the public aware of the critical elements of personal, compassionate, individual care. No government program is going to accomplish this without far more understanding than has been demonstrated to date.

Dehumanized Medical Care

Let us examine the phenomenon of depersonalization and dehumanization of medical care which has been developing over the past several decades. There are essentially three roots: (1) the profession; (2) the public; (3) the government.

There are a number of factors within the profession itself which must be understood. The very fact that the volume of scientific knowledge doubles every ten years is in itself an inevitable force that moves us toward increasing specialization. One should be aware that medical students tend to be disease-oriented and learn about patients as as diseases even before they learn about their patients as human beings. Recognizing that there have been some efforts to correct this, we must still create more methods within our medical schools to focus upon the individual as a whole human being. And we need to center more attention on the *art* of medicine.

The profession itself has problems. Often these problems are personal. They almost always are related to the factor of time. With increased demand for medical services and with increased technological know-how, there often has been an inverse relationship with the time that each physician can spend with each patient. Inevitably, shortcuts had to be taken. Technology certainly can be a tool in our present approach to medical problems. However, a computer which is taking a history with "yes" and "no" answers can hardly recognize the significance of the sudden welling of tears as the patient gives a "no" answer when a "yes" would be correct. Nothing can replace this personal contact of the physician with his patient and nothing can replace the art of the physician who "reads" his patient. Then again, a physician's hard, tough decisions and judgments often, of necessity, must minimize his personal involvement.

The public, on the other hand, has come to have in many instances completely unrealistic and unreasonable expectations of what medicine can accomplish. It is time that we set this record straight. In spite of scientific and technological advancements, organ transplants, miracle drugs, and the like, we must help the public to become more realistic: we cannot always keep a person on the job; we cannot always prevent disability; we cannot always postpone death. In fact, you might say that not one of our patients has ever achieved immortality.

Government Medical Programs

In addition, it is important that the public be acquainted with the true nature of political promises. There never has been a government-financed medical care program which has been adequately funded. Fiscal estimates are always low. I am speaking of the history of the world. Medi-Cal, like other government programs, is over-promised and underfunded.

I am sure that representatives of government would deny responsibility for the dehumanization of medical care present in most government medical care programs. Nonetheless, it isn't difficult to document. First, there is a tendency to treat patients as statistics. They become pawns on a board that are moved around and around with the development of standards of care, often at state and national levels, which deny the individual characteristics of each case, and which ignore vital deviations necessary in some instances. Second, there is an increasing assault on privacy. This loss in the confidentiality of information

should be an issue of national concern. Our profession should join with the press in this matter of extreme public interest. Even now the United States Senate is considering a new code of evidence which would be applied in federal courts throughout the country, abolishing the physician-patient privilege in federal court proceedings with the exception of communications during psychotherapy treatment. Third, there is an increasing pressure for cost containment, not the least important cause of which is the underfunding of political promises.

The results have been restrictions and regulations that decrease the quality of medical care, fail to recognize the true nature of medical practice, and deny individuals as human beings. In the latter instance a case in point is the decision of the state to pay for institutional care at various levels of care. The criteria developed for each "level of care" are silent with regard to the patient's emotional needs. Thus, an elderly patient of mine whose only reason for continuation of an otherwise meaningless existence was visitation by her relatives, was forced to move 40 miles away to a less costly "level of care" upon the decision of a state-employed, non-practicing physician who made his decision without consulting me.

Such practices must cease! Here is where we draw the line. At this point we do become militant, not only as individual physicians but as an organization. And when we make it clear to the public that we are acting in their interests, we shall have the kind of support that will make a practice such as I just described impossible.

Emphasis on Personal Care

All of us must rededicate ourselves to the really personal factors in medical care. We must emphasize again the importance of empathy, of compassion, of conscientiousness, of contact, of caring. Touching means more than physical contact; "the laying on of the hands" means more than faith alone.

After all, is it not our philosophy that individual human beings are the most important things in this world? In our ideology, the state is not supreme; it is the individual. And it is individual dignity and the importance of each living human being that are paramount. Our country enjoys an abundance of goods and services unknown in the rest of the world. That abundance is not the result of government fiat. It is the result of the freedom of each individual to develop his own creativity, so long as he does not infringe on the rights of others. This is truly the mainstream of human progress. Let us never forget that fact as we join in bringing the best of personal, compassionate, human, high quality, scientific care to each individual in this state and nation. By such deeds and actions we shall convince the public that we are not part of the problem, but, rather, part of the solution.

Refer to: Crum JF: Responsible leadership and public confidence—The foundations of a free profession. Calif Med 118:81-83, May 1973

Responsible Leadership and Public Confidence

The Foundations of a Free Profession

JEAN F. CRUM, MD, *Downey*
Immediate Past President, California Medical Association

A LITTLE OVER A YEAR AGO I stood before the 101st Annual Session of this House to assume office as your president. For me personally and for the California Medical Association, these past months have been full ones. They have spanned a period of continued challenge for the medical profession and—through the hard work of a number of people—they have witnessed some important achievements.

When I addressed this House last year, I emphasized that our profession must be prepared for hard choices ahead. And I said, "Society will change, regardless of our actions. Our duty—our responsibility—is to bring our energy to bear on this change, to assure that it serves the best interests of our patients and our nation."

In working to bring our energy to bear on society's patterns of change, we have set as areas of priority: access, quality and cost of health care. While our profession does not by itself have the immense resources necessary to solve the interwoven social and health problems in these areas, we have sought to contribute to their solution. And we have approached these priorities voluntarily—building on the strengths of a health care system proven fundamentally sound.

This voluntary approach is indeed an important aspect of our American way and one of the hallmarks of its great success. Professor Milton Friedman has pointed out: "Political freedom means the absence of coercion of a man by his fellow man. The fundamental threat to freedom is power to coerce." Through the success of our voluntary programs, we can decrease the sources of coercive power and diminish the demands for greater government regulations.

Achievements of Past Year

Last October we had the privilege of presenting the first three certificates in CMA's voluntary program of certification of continuing medical education to the physicians earning them. This was an important milestone and reemphasizes that we have both the opportunity and the obligation to demonstrate the superiority of voluntary programs of continuing medical education. At various national meetings, I have been pleased to note that CMA's prestige and leadership in this field extends to every section of the country.

CMA's work during the past year to strengthen

Address of the Immediate Past President: Presented at the Annual Meeting of the House of Delegates, Califorina Medical Association, Anaheim, March 10, 1973.

Reprint requests to: Mr. David Greer, Division of Professional and Public Relations, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

peer review in California is another excellent example of the voluntary approach. Our CMA Peer Review Commission is a mechanism that *can* act to eliminate the very sources of coercive power. It can help to give the medical profession the strength we must have to play a far more effective role in the arena of health care. But to make it a success each of us must make a personal commitment, and each of us must agree to forego some of his economic prerogatives. It must have the total acceptance and wholehearted cooperation of all our physician members. And time is running out. We may not have another opportunity.

Many of the decisions that affect the future directions of health care are made in the legislative arena and therefore our work in this sphere during the past year deserves emphasis. Our efforts in Sacramento were productive. We continued our work in seeking legislative reforms in the field of professional liability legislation. And we continued to be deeply involved in constructive legislative reforms of the Medi-Cal program. All in all, the 254 bills on which CMA took a position dealt with every phase of health legislation and our cooperative efforts materially benefited the people of California.

On the national level, we have endeavored to inform members of Congress of medicine's viewpoints, objectives and constructive programs. To this end, we have met with California's congressional delegation periodically. We also have held educational seminars for key administrative and legislative assistants to California's congressmen explaining our position on national health insurance, peer review, health maintenance organizations, health manpower and education.

Among other noteworthy developments this past year are the creation of the CMA-Joint Commission on Accreditation of Hospitals Consolidated Hospital Survey Program, the success of CalPAC in representing physician and patient interests politically, the review of long-term care facilities and CMA contributions within the American Medical Association toward making organized medicine more responsive to its members.

These are some of the achievements of the past year to which we can point with pride. But what of the future? What directions should we pursue in the years ahead? History teaches us that the one constant is change itself. The wisdom of the ancient Romans has contemporary significance, "Omnia mutantur nos et mutamur in illis," all things change and we change with them. Today our challenge and our responsibility is to guide that change.

This is not an easy task. We are hampered by politicians seeking personal advantage, by pressure groups, by misinformation given the public, by affluent apathy and lack of cooperation. Moreover, at all levels we see government taking an ever tightening grasp on the mechanisms of health care, centralizing staff and authority, emasculating health programs and budgets. And it is increasingly difficult to influence government in the direction of its health programs and health policies. More and more, government is able to dictate the way we practice medicine and how much we may earn for doing so.

Our freedom as physicians and as citizens is threatened as never before. The question history asks and which we must answer is whether the idea of individualism—the idea of personal freedom for you and me—is equal to the idea of collectivism, the idea of personal subordination to the state.

This ancient contest between freedom and government power, which is renewed in every generation, is acute in ours. Unless we wish to acquiesce to complete government control, we must improve our capability to influence the government policies that affect us. In short, our profession's declining leadership in health care must be given new life.

Leadership and Responsibility

How may this be done? We must recognize that there is a definite relationship between leadership and responsibility. Public opinion ultimately determines the course this nation will follow. All branches of government—legislative, executive and judicial—respond to this force. Our profession's competent self-regulation, our recognized *responsibility*, assures us of public support and increases the strength of our leadership.

We should recognize there are areas in which we can do better. For example, we are continually challenged regarding costs. This can only serve to erode our leadership and diminish public support for our opinions. But such challenges can be silenced by effective programs of cost review supported by every member of the profession. The alternative might well be to price ourselves out of freedom.

Leadership also demands that we operate with a unity of purpose. For us here in California, it means we must be certain that CMA is an or-

ganization broadly representative of all physicians in the state. Different points of view and varying approaches to problems are essential in any healthy and democratic organization. But such differences need not be disruptive. Overall unity of purpose can—and indeed must—prevail.

Unity for the medical profession has become a complicated and difficult task. Over the years medicine has been splintered—by forces operating both inside and outside the profession. Specialty societies, resulting from today's complex medical practice, sometimes have had the effect of dissipating our energies inadvertently by fragmenting the profession. In addition, organizations such as the Physicians Health Congress, the Council of Medical Staffs, the American Association of Physicians and Surgeons, the Medical Committee for Human Rights, the American Public Health Association, as well as physician unions, all seek to represent specific physician interests.

We are faced with a future, then, in which medicine may be represented by hundreds of separate groups working without coordination and each taking a divergent stand on important issues facing the profession. As a result, by abandoning the concept of a unified voice, we abandon the idea of having any voice at all. I hardly need emphasize that with PSRO's, HMO's, PHP's and other ingredients thickening government's alphabet soup, and with Congress slated to renew its debate on national health insurance, our need for unity and a strong voice should be apparent to all of us.

Unity of Health Professions

But even recognizing a unity of purpose within our profession is not enough. We must work to achieve this goal among all of the private elements of the health care system—organizations representing other health professionals and allied professions, health facilities and health insurers. It is essential that we build an effective mechanism to link the various components of private health care so that we may deal with government from the strength of unity—rather than from the weakness of factionalism.

If the health professions act rationally and in concert, we *will* have opportunities to shape the future of health care in California and indeed in America. We have only to recognize that we share a similar destiny. We have only to recognize that together our influence will be magnified if we emphasize our mutual concerns, interests and similarities rather than dwell in a counter-productive fashion upon those issues that divide us. Our professional organizations must be able to support and sustain one another as we build toward a health care system that encourages quality care for all in our society, while assuring us a desirable environment in which to practice according to the dictates of our knowledge and judgment.

Our profession is called upon to organize a new unity in health care. And this summons is a call to our vision, to our humanity, to our practicality. If this can provide the common purpose of all health professions, of our joint enterprise, of our progress together, then we need have no fear for the future.

In order to achieve this significant goal, the medical profession must provide leadership. And if we cannot demonstrate unity ourselves, it becomes impossible to call upon nurses, dentists, hospitals, nursing homes, and health insurers to close ranks with us in the common cause of freedom to provide the best possible care for the patient.

Refer to: Werner SB, Chin J: Botulism—Diagnosis, management and public health considerations (Information). Calif Med 118:84-88, May 1973

Botulism

—Diagnosis, Management and Public Health Considerations

S. BENSON WERNER, MD,
JAMES CHIN, MD
Berkeley

Botulism is an uncommon but often fatal disease associated with ingestion of a potent neurotoxin present in improperly preserved foods. Exposures to commercially preserved foods with an odd or peculiar taste almost never represent exposure to botulism toxin. Improperly prepared home-canned products which are tasted or consumed without heating are more likely to be associated with botulism.

The management of suspect and confirmed cases of botulism is presented by medical epidemiologists in the State Department of Public Health, Bureau of Communicable Disease Control, to provide physicians in California with a practical approach to this problem.

BOTULISM is an uncommon but often fatal illness due to a potent neurotoxin produced by Clostridium botulinum. Spores of C. botulinum are ubiquitous but are not in themselves dangerous when ingested; however, the toxin may be elaborated when spores germinate in an anaerobic environment. Botulinum *toxin* is readily destroyed by boiling but some types of botulinum *spores* are not. Therefore, pressure cooking to reach temperatures of 240°F may be necessary to destroy all C. botulinum spores in certain foods. If some spores survive and germinate, toxin may be elaborated during storage. Disease is usually due to ingestion of preformed toxin in improperly preserved vegetables, fruits, meat or fish products. Botulism has also resulted from wounds infected with C. botulinum in which toxin is produced *in vivo*. Six toxigenic types of C. botulinum are recognized—types. A, B, C, D, E, F. Botulism in humans is almost always caused by A, B or E toxins, and very rarely F. Although types C and D cause botulism in some animal species, these toxin types do not cause disease in humans, with possible rare exceptions.[1]

A recent publication[2] shows that between 1899 and 1969, there have been 659 outbreaks of botulism comprising 1,696 cases. A total of 234 (34 percent) of the outbreaks were reported from California. The reasons for this disproportionate percentage for California's population are speculative, and may include a greater awareness of botulism due to Meyer's work[3] or perhaps a greater concentration of botulism spores in California soil than elsewhere. Type A botulism has accounted for 72 percent of typed outbreaks nationally; in California, type A accounted for 87 percent, B for 7 percent, E for 1 percent, F for 1 percent, and A and B together for 3 percent. The state's only documented type E outbreak occurred in 1941 and was traced to imported commercially grown mushrooms canned in San Francisco.[4] The nation's only

From the Bureau of Communicable Disease Control, California State Department of Public Health.

Reprint requests to: S. B. Werner, MD, California State Department of Public Health, 2151 Berkeley Way, Berkeley, Ca. 94704.

type F outbreak occurred in California and was traced to home-prepared venison jerky.[5]

The botulism case fatality rate has decreased in recent years. Nationally, it was 60 percent between 1899 and 1949, but less than 30 percent between 1960 and 1969.[2] The incidence of botulism has also decreased since 1940.[2] As a result of high and improving standards in the canning industry, this disease is much less frequently due to commercial foods than it was in earlier years. In the United States between 1960 and 1969, ten outbreaks of botulism associated with commercially processed foods were reported; these represented only 13 percent of all outbreaks of botulism during that period. Most of the outbreaks from commercial foods since 1960 were due to improperly preserved—not canned—fish or meat products. California's cases of botulism have been due primarily to faultily home-canned or preserved vegetables. See Table 1.

TABLE 1.—*Botulism Cases by Source California, 1950-1971*

	Cases
Food, Home Processed	
Fruits and Vegetables*	74
Tuna	4
Deer Jerky	3
Pickled Pigs Feet	1
TOTAL	82
Food, Commercially Processed	
Cheese	1
Chopped Chicken Liver	1
TOTAL	2
Wound Infection	4
Unknown	8
TOTAL CASES	96

*Includes mushrooms 15, olives 7, chili peppers and beans 16, fruits and fruit juices 7, tomatoes 4, figs 4, okra 2, corn 1, stringbeans 2, cactus 2, beets 1, par par 3, avocado sauce 1, choyote 1, potatoes 1, black-eye peas 3, squash 1, "vegetables" unspecified 1, "Korean vegetable dish" 2.

SOURCE: State of California, Department of Public Health, Morbidity Records.

Diagnosis

Clinical Presentation

Incubation periods reported in the literature range from six hours to eight days, with an average of 12 to 36 hours. In recent years the extremes have not been encountered in California and most cases had incubation periods of 12 to 48 hours.

Presenting complaints generally consist of: (1) ptosis, (2) blurred or double vision, and/or (3) dry, sore throat; sometimes all three. In the 1971 Bakersfield outbreak[6] involving five cases, several persons presented with sore throat as their chief but not sole complaint.

Vital signs (blood pressure, temperature, pulse, respiration) are remarkable for their normality when patients are first seen, though postural hypotension may sometimes be exhibited. Fever is conspicuously absent unless secondary complications such as pneumonia or urinary tract infection supervene. Arrhythmias occasionally occur, but they have not been observed as a prominent part of the clinical picture. Respiratory difficulty is not usually present with initial symptoms.

Neurologic factors. Weakness or paralysis in botulism is most frequently of the descending type. Paralysis is usually but not always symmetrical. There is early ptosis and eye muscle involvement, with limited motion of extraocular muscles, strabismus, and nystagmus on testing. Pupils may be fixed and dilated. There may be dizziness, facial paralysis, dysphonia, dysphagia, and inability of the neck muscles to support the head. Disease may progress to quadriplegia and respiratory failure, but no patient developed respiratory symptoms to our knowledge without first having cranial nerve deficits, nor has respiratory difficulty been a sudden development.

Deep tendon reflexes are frequently depressed symmetrically, or absent. Conspicuously absent is any objective sensory disturbance despite profound motor abnormalities that may be in evidence. Paresthesia and decreased tactile perception are not part of the neurologic picture of botulism, nor is there any subjective discomfort (pain, tenderness) at paralyzed areas. Abdominal pain due to paralytic ileus may develop, with attendant constipation. Headache and retrosternal burning have been reported, but the pain we have most commonly noted in botulism is that associated with the pharyngitis mentioned earlier. In conjunction with this symptom, mucous membranes of the mouth and pharynx are found to be dry and erythematous. In some cases botulism has been initially misdiagnosed and treated as "strep throat."

Despite the *appearance* of lethargy given by ptosis, flexed neck while sitting, and difficulty in communicating verbally, the toxin does not affect the sensorium; mental clarity remains intact in botulism unless complications develop. Only rarely do patients with botulism have gastrointestinal symptoms of nausea, vomiting, abdominal cramps or diarrhea; these are, however, more likely to occur with type E botulism than with types A and B.

TABLE 2.—*Paralytic Diseases Confused with Botulism*

Disease	*Features distinguishing this disease from botulism*
Cerebrovascular accident involving midbrain	Localized signs, sensory deficits, asymmetric deep tendon reflexes
Polio and other encephalitides	Fever, altered mental state, abnormal CSF
Guillain-Barré syndrome	Ascending paralysis, paresthesia, pain, abnormal CSF
Myasthenia gravis	Muscular fatiguability, positive Tensilon test
Tick paralysis	Presence of a tick, paresthesia of affected extremities
Paralytic shellfish poisoning	Incubation period 15-60 minutes, paresthesia
Carbon monoxide poisoning	Altered mental state, cherry-colored skin
Organic phosphate poisoning	Fever, altered mental state, miosis, increased oral and respiratory secretions, fasciculations, muscle cramps, paresthesia, depressed serum cholinesterase
Antibiotic paralysis (kanamycin, streptomycin, neomycin, etc.)	Secondary to antibiotics administered under general anesthesia
Poisoning with belladonna-like alkaloids	Fever, tachycardia, altered mental state

Laboratory Studies

An attempt should be made to confirm suspicion of botulism by demonstrating that the patient's serum is toxic for mice. Before botulism antitoxin is administered, at least 10 ml of serum should be collected and refrigerated until delivered to the laboratory. Preliminary test results are usually not available for 24 hours and cannot be used initially to decide whether or not to administer antitoxin. If treatment is clinically indicated, antitoxin should be administered without delay.

Type A toxin may not be detected sometimes even when serum is collected early, possibly because of its rapid removal from circulation and early fixation to nerve tissue.[7] Type E and B toxins can circulate for much longer periods; they have been detected in serum as long as 10 and 22 days, respectively, after ingestion.[7] In situations involving clinically suspect botulism, suspect food(s) and their containers—even when empty—should be collected immediately, refrigerated, and tested for botulism toxin as soon as possible. In situations where only possible exposure to botulism is considered, toxicity testing of commercial food is usually not indicated (see public health management, below).

Cultures of stool specimens are not worthwhile. Clostridium botulinum is rarely isolated; when it is, its relevance to the problem is questionable. Necropsy studies have revealed no specific histopathologic appearance of nerve tissue or other tissues.

Routine laboratory studies including complete blood count, sedimentation rates, and blood chemical determinations are not helpful in the diagnosis of botulism. Urinalysis has, at times, shown proteinuria but this finding is nonspecific. Studies of cerebrospinal fluid are remarkable in being within normal limits. Chest x-ray films may show elevation of the diaphragm secondary to diaphragmatic paresis and atelectasis. Electrocardiograms may show nonspecific ST-T wave abnormalities, bundle branch blocks or arrhythmias.

Differential Diagnosis

Diseases which may cause acute paralytic illness are frequently confused with botulism: Guillain-Barré syndrome, carbon monoxide poisoning, encephalitis, myasthenia gravis, and cerebrovascular accidents are the most common. These and other diseases may be distinguished from botulism by key features noted in Table 2, which incorporates the most likely paralytic diseases encountered in a differential diagnosis. References should be consulted for detailed descriptions of these and other conditions.

Management

Public Health Management

Suspect cases of botulism, and cases of exposure to suspicious foods, should be reported to the local health department immediately. Prompt investigation is necessary to determine whether botulism is a possible problem so that suspect foods can be identified and eliminated as a continuing hazard. Health department staff will attempt to contact all persons known or suspected of having been exposed, to obtain detailed food histories and refer them for medical care. In addition, health department personnel will search the home or other sites of probable exposure to recover suspect foods and containers for appropriate laboratory study.

Clinical Management

The asymptomatic case with questionable exposure. Concern about botulism generally arises when an individual reports tasting or consuming a commercially canned food from a can that was bulging or whose contents tasted peculiar. Such bulging often represents an overfilled can, and detailed questioning frequently reveals that the

"explosion" on opening such cans is of fluid under pressure, not gas. Even when the cans are gaseous, the gas may merely be the result of chemical reactions subsequent to de-tinning of the can lining. Where foods are boiled before consumption, exposure to botulism toxin can be ruled out since the toxin is heat-labile. However, if such foods are not heated before ingestion, then potential for disease exists if toxin was present.

While these experiences with commercially canned foods almost never represent exposure to botulism toxin, it is advisable nonetheless to recommend evacuation of gastrointestinal contents as a precautionary measure. Vomiting should be induced or aspiration and lavage performed. A cathartic should be administered, and possibly an enema, too. As botulism toxin, once formed, is less stable at alkaline pH, it would appear reasonable to lavage with $NaHCO_3$. The administration of botulinum antitoxin carries some risk, and so its use is not advised in situations of questionable exposure. The patient may be followed as an outpatient under close medical observation. Such patients have generally not had exposure to botulism, and almost invariably no further action is necessary.

The asymptomatic case with probable exposure to botulism. This situation generally arises in a setting in which clinical cases of botulism are known to exist and where an asymptomatic person is suspected of having consumed the same incriminated food or meal. Asymptomatic patients in such a situation should be put into hospital for closer medical observation, and gastrointestinal contents should be evacuated as outlined in the section above. Serum should be obtained for mouse toxicity studies. The decision, however, to administer botulinum antitoxin to asymptomatic persons should be weighed carefully against the risks of potential anaphylaxis and serum sickness. Intensive observation may well be the safer course. However, at the first indication of possible symptoms of botulism, prompt treatment with antitoxin should be initiated.

The symptomatic case with suspected botulism. Admission to hospital, evacuation of toxin and antitoxin treatment.

On suspicion that a patient has developed signs and symptoms of botulism, it is imperative that he be put into hospital immediately—preferably in an intensive care unit. Efforts at eliminating toxin from the gastrointestinal tract should be undertaken as prescribed above. Pre-treatment serum should be obtained for mouse toxicity studies. Skin test for sensitivity to horse serum should be done as indicated on package inserts, then botulinum antitoxin administered promptly. If sensitivity to to horse serum is demonstrated, desensitization should be carried out according to instructions on the package insert. The earlier the initiation of antitoxin treatment, the better the prognosis.

Approximately 98 percent of typed botulism outbreaks in California since 1899 were type A, type B or both. Therefore, bivalent (AB) antitoxin will ordinarily be appropriate. Bivalent antitoxin is commercially available in California only from Lederle Laboratories in Los Angeles, phone (213) 723-6411 or (213) 722-3822. Trivalent (ABE) antitoxin, produced by Connaught Laboratories in Canada, is available from the Center for Disease Control, Atlanta, Georgia. An emergency supply of this antitoxin is kept at the State Health Department in Berkeley, phone (415) 843-7900. Trivalent antitoxin, because it includes type E antitoxin, is preferable until toxin type is determined. Type E antitoxin is especially important when the peccant food is from out-of-state—particularly fish from the Great Lakes area, Alaska or Japan. In California, the first dose of antitoxin may be either AB or ABE, depending on availability; subsequent doses of antitoxin ideally should be trivalent (ABE) unless laboratory results indicate A or B toxin, in which case the bivalent antitoxin can be used.

The potency of Connaught's 8 ml vial of ABE antitoxin in international units is A 7500, B 5500, E 8500; Lederle's 30 ml vial of AB antitoxin has A 10,000 and B 10,000. We recommend treating clinical cases with intravenous antitoxin, one vial every four hours until a total of four or five vials of ABE antitoxin or three or four vials of AB antitoxin has been administered. The antitoxin will bind circulating toxin and thereby prevent progression of neurologic symptoms, but it cannot undo paralysis already present. Serum may be tested subsequently for circulating toxin, and if toxin is detected additional antitoxin should be given. We have not observed persistence of circulating toxin in persons so treated. Follow-up testing for circulating toxin should be mandatory in cases of wound botulism to rule out continued elaboration of toxin in infected wounds.

If patients with botulism are first seen several days after onset of symptoms and there has been no progression at all of signs or symptoms in the preceding day or two, the administration of anti-

toxin may have little value, particularly when type A toxin is involved.

Guanidine hydrochloride—a drug currently under investigation—has been used to treat botulism. The similarity between the neuromuscular blocks of botulism and the Lambert-Eaton syndrome (for which guanidine has been of clinical value) prompted Cherington and Ryan[8,9,10] to investigate guanidine therapy for botulism. While they described favorable clinical responses such as increased vital capacity and improved extraocular movements following its use, a more recent study did not show any clinical benefit from guanidine.[11] Its role as an adjunctive measure in the treatment of botulism needs further study.

Attention to respiratory function has been at least as important as antitoxin therapy in reducing the case fatality rate in recent years. The immediate danger to the patient with botulism is respiratory insufficiency.[12] Accordingly, some feel that "early elective tracheostomy is mandatory."[13] However, since respiratory difficulty does not develop abruptly, it appears more reasonable to delay intubation until there are signs of impending respiratory difficulty. Even then, endotracheal intubation may be sufficient in mild cases, and safer when employed for no more than one week. In view of frequent complications (such as hemorrhage and infection) when tracheostomies are performed in hospitals with limited facilities and staff, serious consideration should be given to the possibility of transferring the patient immediately to a center proficient at inhalation therapy and intensive nursing care.

Respiratory function should be monitored by measurements of vital capacity and arterial blood gases. Pulmonary consultation should be obtained as soon as possible. If it appears that respiratory assistance will be needed, mechanical respiration with a tank respirator, an intermittent positive pressure breathing apparatus, or a volume respirator should be considered.

Inhalation therapists, physical therapists, chest physiotherapists and intensive nursing care play paramount roles in continuing clinical management. Frequent aseptic tracheal suctioning with disposable catheters, adequate humidification of inspired gases, attention to postural drainage, and continuous ventilatory support may prevent the occurrence of pneumonia. (Pneumonia developed in more than 50 percent of botulism patients with tracheostomy seen in California in the past several years.) If the patient's pulmonary function can be satisfactorily maintained and he can be kept alive, full neurologic recovery can be expected, although it may take months.

Ancillary Measures. On admission, a base-line electrocardiogram should be taken in all cases. Cardiac monitoring should be considered, and certainly it should be employed when heart block or an irregular rhythm is present. Urinary retention is a frequent occurrence, but it is best to wait until the need is demonstrated before insertion of an indwelling catheter. Even then, suprapubic cystostomy may be preferred. Antibiotic therapy should be reserved until development of such complications as respiratory or urinary tract infections. To prevent pulmonary aspiration, the patient should receive nothing by mouth until pharyngeal paralysis disappears. If aspiration of oral or gastric contents occurs, penicillin should be instituted immediately. Corticosteroids should also be given if less than 24 hours have intervened since aspiration of gastric contents in order to suppress pulmonary inflammatory reaction. The prolonged adynamic ileus sometimes seen in botulism may necessitate hyperalimentation infusions, via a central venous cannula, until bowel sounds return and nasogastric tube feedings can be instituted. Alternatively, a temporary feeding gastrostomy may be considered if bowel sounds are present.

Finally, as with all bedridden patients, attention should be given to maintaining adequate nutrition and muscle tone while preventing decubitus ulcers, contractures, thrombophlebitis and constipation. With proper supportive care, each botulism victim can expect complete neurologic recovery.

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The Clinical Significance of the SGOT Test

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ALTHOUGH THE HISTORY and physical examination performed with patience and care remain the cornerstone of successful medical practice, the modern physician must also rely on laboratory tests for confirmation of clinical impressions and monitoring of therapeutic endeavors. Advances in laboratory technology now allow for a battery of tests to be done on one specimen of blood and often provide us with unanticipated abnormal results that must either be ignored or somehow explained. We are anxious about "missing something," and yet we hope to avoid what Rang[1] has labeled the Ulysses syndrome—the mental and physical disorders which befall a patient as his physician attempts to track down the cause of a falsely positive laboratory result.

In these circumstances it seems timely to discuss the clinical significance of the serum glutamic oxalacetic transaminase (SGOT) test, a common component of most biochemical screening panels. In three recent studies of large patient populations,[2-4] the SGOT was abnormal in 1 to 4 percent. Friedman et al[3] reviewed the results of a 20-test screening panel drawn on 8,446 persons having a "multiphasic health checkup" in the context of the Kaiser-Permanente program in Oakland and San Francisco. Of 7,512 SGOT tests 202 (3 percent) were abnormally high. In a study of 547 patients seen in the General Medical Clinic of the Stanford University Medical Center, Schneiderman et al[2] found seven, or about 1 percent, to have abnormal SGOT tests. Finally, Bates and Yellin[4] analyzed all results from a large multiphasic screening unit in the Rochester, N.Y., area and noted 4 percent of the SGOT values to be elevated. My own experience has been similar and will be discussed below.

As has been pointed out by other investigators,[2,5] the statistical "normal" of any given test refers to values lying within two standard deviations from the mean; that is, between the 2.5 and 97.5 percentile points "of the distribution of values for healthy persons." It follows, then, that occasionally, or one time out of 20, the test in question will fall outside the normal range without indicating a true abnormality. The normal range for a test will vary according to the control population and specific laboratory method used for its determination.

Method

Several exhaustive reviews have been published regarding the nature of the GOT enzyme and the methods for determining how much of it is present.[6-12] For the purposes of this brief clinical review, it need only be remembered that this enzyme catalyzes the transfer of an amino group from an alpha amino acid to an alpha keto acid—that is, a transamination reaction:

$$\text{aspartic acid} + \text{ketoglutaric acid} \xrightleftharpoons{\text{SGOT}} \text{oxalacetic acid} + \text{glutamic acid}$$

The enzyme is found throughout the body, especially in the heart, liver and muscle tissues.[6-12] Its concentration in the serum depends on the amount originally in the normal or injured tissue, the rate of cellular release, and the rate of removal from circulation.[8] Injected glutamic oxalacetic transaminase distributes throughout body fluid and very little is lost in the bile or urine.[13] Presumably the enzyme is metabolized and degraded within the body.

Measurement of serum enzyme activity can be done by chromatographic,[6] spectrophotometric[7] or colorimetric methods.[11] Most automated screening panels have used diazonium salts to give the colorimetric reaction, and it is now clear that interfering substances in the patient's blood such as acetone or drugs may give falsely elevated results.[14-16] Determinations based on the manual

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spectrophotometric method of Karmen[7] which involve the oxidation-reduction of nicotinamide adenine dinucleotide (NAD) are less likely to give spurious results, and are being incorporated into the screening panel methods of some laboratories.

Clinical Significance of SGOT

As noted above, 1 to 4 percent of serum specimens from several outpatient populations showed elevated SGOT. My own experience has been similar. Twenty-five of 350 consecutive patients (7 percent) seen over a recent 12-month period for annual examinations had elevated SGOT on the sequential multiple analysis (SMA) 12/60 multiphasic panel which uses a colorimetric procedure with "normal" being up to 50 units. None had values higher than 150 units and most were under 100. Two of the 25 patients could not be traced for further evaluation. In the remaining 23 patients, however, repeat SGOT determinations done manually by the Karmen method were normal in 18 and still abnormal in five. Of the latter, one proved to have chronic hepatitis on liver biopsy, and the other four had a return to normal values after stopping all alcohol ingestion for one month.

When confronted with an abnormal SGOT on a screening panel, one should first repeat the test, using the specific NAD-linked method if at all possible. More often than not, the repeat value will be normal. Elking and Kabat[14] listed 34 drugs which they feel can falsely elevate SGOT test values. Other observers have described spurious elevations of the SGOT when measured by the colorimetric method in patients taking erythromycin[15] or para-aminosalicylic acid.[16]

Repeated intramuscular injections of drugs, by damaging muscle, may also elevate the SGOT.[17] Knirsch and Gralla found elevations to levels of 115 units after three days of parenteral carbenicillin. I have seen several similar cases. Values return to normal within a week or two of stopping the injections, and the CPK (creatine phosphokinase), an enzyme not elevated in liver disease, also rises at the same time.

To this point, discussion has revolved around the presumably healthy person with an unanticipated elevation in their SGOT. What is the approach when the patient is obviously ill? There should be little difficulty in evaluating an elevated SGOT in patients with acute tissue damage from myocardial infarction, viral or drug-induced hepatitis, or muscle inflammation. In my experience, the clinical picture in these common causes of SGOT elevation is usually clear, and the diagnosis can be readily confirmed by utilization of other appropriate laboratory tests.[18-23]

Certain other diseases, or medical events, however, which can occur in sick patients may elevate the SGOT and cause considerable confusion unless recognized.

It is common to administer opiates to patients with abdominal pain. Shuster et al[24] showed that codeine, meperidine, or morphine did not elevate the SGOT when given to healthy students. It is quite clear, however, that if these drugs are given to patients with either a nonfunctioning or absent gallbladder, the SGOT will be elevated to levels ten to twenty times normal.[25-27] The rise starts within two to four hours of the injection and is usually back to normal by 24 hours. Presumably these opiates increase biliary pressure by inducing spasm at the sphincter of Oddi. The lack of a normal gallbladder reservoir allows the increased pressure to be exerted on liver cells with subsequent injury and leakage of the enzyme. Thus, serum should be drawn for later laboratory tests before opiates are administered to a patient with abdominal pain.

The SGOT is often very helpful in deciding whether a patient with jaundice has intrahepatic or extrahepatic disease. Nonetheless, occasionally extrahepatic obstruction will markedly elevate the SGOT and cause diagnostic confusion. Abbruzzese and Jeffery[28] reported three patients with common duct stones who showed SGOT values of 1,320, 1,250 and 960 units soon after admission. Ginsberg[29] likewise noted three similar patients with SGOT values of 1,710, 2,450, and greater than 1,250 units secondary to extrahepatic biliary tract obstruction. In reviewing the literature, he found the incidence of an SGOT value greater than 300 units in extrahepatic obstruction to be about 3 percent (6 of 176 cases). Thus not all jaundiced patients with an SGOT value higher than 500 units will have hepatitis. Clues to the elevation's being secondary to extrahepatic disease are the rapid fall toward normal (below 300 units by day 3 to 4) and the accompanying pronounced elevation in the lactic dehydrogenase (LDH) values.

Acute pancreatitis may raise the SGOT also. Foulk and Fleisher[30] found 22 of 32 patients with pancreatitis to have elevated serum levels depending on the severity of associated biliary tract inflammation. There was no correlation with the severity of the pancreatitis per se. Seven of the

22 had levels higher than five times normal, and one measured approximately 700 Karmen units.

SGOT values higher than 1,000 units are usually due to viral or drug-induced hepatitis. As mentioned above, another cause may be extrahepatic obstruction. Shock and congestive heart failure may also lead to extremely high levels of SGOT. I have seen several patients in severe heart failure with values higher than 2,000 units. Fragge et al[31] reported in 1960 that one-third of their patients with heart failure had elevated SGOT values. They noted levels of SGOT in a literature review ranging from 45 to 750 units, with a few cases greater than 2,000. Logan et al[32] reported three cases of severe heart failure with SGOT values of 1,180, 1,780, and 1,300 units. They felt the cause might be two-fold: liver congestion, and also anoxia from decreased oxygen concentration and blood flow in the hepatic artery.

One may be asked to see a patient with elevated SGOT in the immediate postoperative period. Besides the numerous causes already alluded to, question arises as to the role of surgical operation per se. Ayres and Williard[33] studied 266 patients after operation. They found 20 percent to have a slight elevation of SGOT over the first four days. Levels were usually less than 120 units, with a few as high as 250 units, and all were back to normal by day 5.

In conclusion, the advent of biochemical screening panels has confronted the clinician with an array of unexpected abnormalities in presumably healthy patients. Because of the presence of SGOT in tissues, often effected by serious disease, and the inclusion of the test on most panels, the results of the test must be reckoned with. One should first ascertain if the reported value is truly or spuriously elevated. In my experience, if the patient is asymptomatic and the results of physical examination are within normal limits, the commonest cause of elevation is alcohol abuse or drug ingestion. If the patient is ill, diseases of the heart, liver or muscle are usually the cause of the increased values, but one must remember that substantial elevations of the SGOT can occur in patients who have been given opiates, or who are ill with extrahepatic obstruction, congestive heart failure, or shock.

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Immunizations and Prophylaxis for Foreign Travelers

IMMUNIZATION REQUIREMENTS and recommendations for foreign travel are in a constant state of flux depending on current epidemic patterns of communicable disease. In addition, risk of exposure will depend on whether or not the traveler will be staying briefly at resort hotels or dwelling abroad for longer periods. In either case local health department officials can assist regarding the most up-to-date information.

Only smallpox, yellow fever, or cholera immunizations can be required as a condition to entry into a country. These immunizations, when required, must be properly noted and validated on an International Certificate of Vaccination. All other suggested immunizations are merely "recommended." However, for the traveler's own health, these may be more important than the required immunizations.

Whenever a required immunization is medically contraindicated, a physician may provide his patient with a signed and dated statement on his letterhead stationery detailing the contraindication. Examples may include skin disorders (smallpox), pregnancy, altered immune states, and the like. Such a statement will usually be honored by most governments.

At this time, no immunizations are required or recommended for United States travelers who go only to one of the following: Europe (eastern or western—except England, where, because of cases occurring in April 1973, it would be best to recommend temporarily), Russia, Canada, Mexico, Caribbean Islands, Australia, New Zealand, and Tahiti.

The traveler's entire itinerary must be considered, since smallpox immunization may be required by the above countries if the traveler does not come directly from the United States—for example, Australia will require smallpox immunization if the United States traveler goes to Europe or Russia first.

Smallpox Immunization. No longer required for reentry into the United States unless travel has actually occurred in an infected area. However, required by most foreign countries except as noted above. Vaccination is valid for three years.

Cholera Immunization. Not required for reentry into the United States even if travel has occurred in an infected country. However, most foreign countries do require it of anyone who has been in an infected area. Two immunizations are recommended even though a complete series has been given in the past, not on medical grounds, but rather because some travelers who have had only boosters have experienced difficulty in travel to some countries. Immunization is good for six months. Recently infected areas have included the Philippines, Southeast Asia, Burma, India, the Middle East, and most of Africa north of the Republic of South Africa, including Angola and Kenya.

Yellow Fever Immunization. The endemic areas include, in general, African countries that border on the equator and extend as far as 15° latitude north and 10° south, including the country of Angola. (Endemic countries frequently visited include Kenya, Tanzania, Ethiopia.) In addition, all or part of the countries of Panama, Venezuela, Colombia, Ecuador, Peru, Bolivia, Brazil (northwest portion only), Guyana, Surinam and French Guiana in South America are considered endemic areas.

Poliomyelitis Immunization. Not necessary for Australia, New Zealand, Tahiti, Canada, Western or Eastern Europe, Russia and the usual tourist areas of Mexico. This immunization is recommended for most other international travel. A single or one time "booster" of trivalent oral poliomyelitis vaccine is recommended for adults who have had a primary series.

This report of current information was prepared at the behest of the Advisory Panel to the Section on Preventive Medicine and Public Health.

Typhoid Fever Immunization. Not recommended for travelers who stay at the usual tourist accommodations in most European and Caribbean countries. It is recommended for travelers to Guatemala and countries south in the Americas, Africa, Asia, and the Middle East, and the Pacific region (the area north of Australia). Because of the recent epidemic around Mexico City, immunization is recommended for travelers to Mexico, except those going to Baja California and staying at the usual tourist places there.

Plague Immunization. Not routinely recommended. It is recommended for travel to Vietnam, Cambodia and Laos.

Typhus Immunization. Not routinely recommended. Consider only for those who will be going to remote highland rural areas and living closely with the natives in an area where the louse-borne disease is endemic—for example, might be considered for missionaries, anthropologists, and the like.

Infectious Hepatitis. An active immunization agent does not exist. However, passive immunization by means of immune serum globulin should be considered for travelers to either tropical areas or developing countries, but it is not indicated for travelers to Europe, Canada, Caribbean Islands, urban Mexico, Australia, Japan, New Zealand, Tahiti, or Fiji. Recommended dosage for adults is 2.0 ml if staying in endemic areas less than three months, and 5.0 ml if staying more than three months. Correspondingly smaller doses based on body weight are used for children.

Malaria. Endemic areas include Africa, Haiti, Central America, the southern west coast region and southern states of Mexico; South America with the exception of Venezuela, Uruguay, Chile and Argentina; the southern Middle East; Southeast Asia; Korea and some of the islands of the Southwest Pacific region. With the exception of tropical Africa, antimalarial prophylaxis usually is not indicated when only major cities will be visited. For adults 500 mg (300 mg base) chloroquine phosphate (Aralen®) once a week, starting the week before exposure and continuing for at at least six weeks after exposure is discontinued, is recommended. Alternate drugs are hydroxychloroquine sulfate (Plaquenil®), chloroquanide hydrochloride (Paludrine®), and pyrimethamine (Daraprim®). For those who have been bitten heavily by mosquitos in an area endemic for relapsing species, primaquine phospate 26.3 mg (15 mg base) for adults, daily for 14 days after discontinuance of chloroquine should be considered. Areas endemic for relapsing species include Central and South America and Asia.

African Sleeping Sickness (Trypanosomiasis). No immunization or prophylaxis is available. Endemic areas include West and East Africa. Cases have occurred in California residents after visits to game parks in Rwanda and Botswana. If exposure cannot be avoided, appropriate protective clothing should be worn to avoid the bite of the tsetse fly. Insect repellents may also be helpful.

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PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Director, State Department of Public Health

Intermediate Care Facilities

INTERMEDIATE HEALTH CARE facility regulations adopted by the State Board of Public Health in 1970 and 1971 were designed to provide a sheltered living environment, including board, room, social-recreational programs and limited health care or observation for resident patients, defined as persons who, because of a physical or mental condition or both, require intermittent nursing care. Resident patients do not in the opinion of their physicians have an illness, injury or disability for which continuous nursing services are required and they exclude: (1) persons with a communicable disease; (2) mentally disturbed persons who require locked doors or constant supervision; (3) mentally retarded persons requiring special services not usually available in any but specialized facilities; (4) persons requiring skilled nursing care and observation 24 hours a day; (5) those requiring daily care by a physician.

Regulations concerning administration of intermediate health care facilities include a requirement that policies governing personal care shall be developed with the assistance of a physician, a registered nurse, a qualified social worker and other personnel who are considered appropriate. Persons employed in these and other facilities must be free from communicable diseases. A health examination is a requisite for employment unless the employee presents written evidence that an examination has been completed within six months of the start of employment.

Intermediate care facilities may exist as separate physical entities or they may be units in hospitals or nursing homes. Within these institutions, units of fewer than 50 intermediate care beds are not required to provide licensed personnel in addition to those already on duty. Units of 50 or more intermediate care beds must provide a registered nurse or licensed vocational nurse employed full time during the day shift. Separate facilities and those which are part of existing health care facilities, are not required to have nursing personnel on night shifts, but a way for residents to signal attendants from their bedside must be provided.

The number of patients in California's 1,200 nursing homes at any given time is about 65,000 with 6,000 to 7,000 persons entering these facilities each month except just before the year-end holidays and at the start of summer. Intermediate care units have been established in 260 nursing homes and there are eight separate intermediate care facilities in the state. At present, approximately 4,000 resident patients occupy intermediate care beds, according to the Department of Health Care Services, which conducts 6,000 to 6,500 annual reviews of patient status per month. About eight percent of the California nursing home population is reclassified each year for intermediate care but not all of those who are reclassified are transferred. Of the 20,000 to 24,000 reauthorization requests received by the Department each month, about 1.5 percent are reclassified; more patients might be moved into intermediate care facilities, but without adequate field inspection resources of its own the state depends exclusively on the statements of nursing home patients and recommendations of attending physicians.

State reimbursement to nursing homes under present Medi-Cal regulations ranges from $15.33 to $16.37 per day, with an average reimbursement of $15.80 per day. Intermediate care reimbursement, whether in a nursing home or separate facility, is $10 per day. State Department of Social Welfare residential care reimbursement rates vary from county to county, averaging about $220 per

month for patients requiring a higher level of care; this figure includes supplementary payments by the counties. Total nursing home reimbursements for fiscal year 1971-72 were $227,753,532; for 1972-73 a total cost of $253 million is projected by the Department of Health Care Services. An additional $1,990,530 was spent for intermediate care resident patients in the three-month period ending January 1, 1972. No data are available from the Department of Health Care Services on the number of Medi-Cal recipients in residential care facilities.

Medical-social review teams from the Medi-Cal agency continue to consult with nursing home patients and their physicians to determine if an individual's health care needs can be better met at another level of care. The findings of the teams are also discussed with members of the patient's family if they are available. When a decision is made by the team and the attending physician to terminate Medi-Cal coverage of nursing home care, a medical-social review social worker and a county welfare department social worker locate an appropriate, certified intermediate care or residential care facility. Reclassification of a nursing home patient does not affect eligibility for Medi-Cal. If a request by the patient for a fair hearing is received before the effective date of nursing home care termination, the Department of Health Care Services will continue paying for care until a decision is issued.

Nursing home patients eligible for reclassification may choose to receive care in any state-certified intermediate care facility but the state will not pay for care in a non-certified facility. The Department of Health Care Services states in a "Questions and Answers" leaflet distributed to nursing home patients that "an intermediate care facility is primarily a residence, but a residence for people who need a certain amount of health supervision." A resident patient is required to have an attending physician, and a trained nurse is on duty during daytime hours. Assistance is provided with personal hygiene tasks such as bathing and shaving, and resident patients are helped in eating, getting out of bed and moving about. Intermediate care facilities, in addition, are required to maintain standards of physical safety and patient security maintained by nursing homes.

The Department of Health Care Services, in its statement to nursing home patients, says that they do not have to move out of an intermediate care facility because of a minor or temporary illness. On the other hand, if a major illness or disabling physical problem develops that will require long bed rest or almost constant care, the intermediate care resident patient will be moved to a hospital or nursing home. The intermediate care resident with average health is encouraged to use the facility as an intermediate step between the hospital or nursing home and his own home or residential care facility. The aim of intermediate care, in the Department's words, is "to help everyone move toward independence." It is designed to allow the resident patient as much freedom and activity as the patient and the attending physician agree is reasonable.

The Department of Public Health and the State Board of Public Health endorse the concept of intermediate health care, and encourage physicians in California to investigate its rehabilitative potential.

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1. California Health and Safety Code, Sections 102, 208 and 1411
2. California Administrative Code, Article 4, Section 385.5, Title 17
3. California Administrative Code, Article 8, Section 389.6, Title 17
4. Personal Communication, State Department of Health Care Services

In Memoriam

ALCABES, JACOB-MEIR, Santa Monica. Died October 20, 1972 in Santa Monica of cerebral vascular accident, aged 48. Graduate of Universidad Mayor de San Marcos de Lima Facultad de Medicina, 1950. Licensed in California in 1966. Doctor Alcabes was a member of the Los Angeles County Medical Association.

ATWOOD, JOHN M., Yuba City. Died October 1, 1972 in Marysville of pulmonary infarction, aged 51. Graduate of Washington University School of Medicine, St. Louis, 1945. Licensed in California in 1967. Doctor Atwood was a member of the Yuba-Sutter-Colusa County Medical Society.

BOWMAN, KARL M., San Francisco. Died March 2, 1973 in San Francisco, aged 84. Graduate of Los Angeles Medical Department, University of California, 1913. Licensed in California in 1913. Doctor Bowman was a member of the San Francisco Medical Society.

DIEUDONNE, CHARLES C., Murphys. Died January 4, 1973 in Murphys of overwhelming toxemia after five years' support by renal dialysis, aged 57. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1942. Licensed in California in 1942. M.D. degree from California College of Medicine, 1962. Doctor Dieudonne was a member of San Joaquin County Medical Society.

HALL, MELVYN D., Santa Cruz. Died March 14, 1973 in Santa Cruz, aged 38. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1959. Licensed in California in 1960. Doctor Hall was a member of the Santa Cruz County Medical Society.

NELSON, WILLIAM NEWTON, Fillmore. Died March 3, 1973, aged 81. Graduate of the University of Nebraska College of Medicine, Omaha, 1925. Licensed in California in 1934. Doctor Nelson was a retired member of the Ventura County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

POWELL, DEWEY ROBERT, Stockton. Died November 11, 1972 in Stockton of arteriosclerotic heart disease, aged 84. Graduate of the University of California Medical School, Berkeley-San Francisco, 1912. Licensed in California in 1912. Doctor Powell was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

RASMUSSEN, GLENN S., Novato. Died March 6, 1973 in San Francisco, aged 59. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1950. Licensed in California in 1950. Doctor Rasmussen was a member of the Marin Medical Society.

RENSHAW, DEAN LEWIS, La Mirada. Was killed March 21, 1973 in the crash of a light plane near Fullerton, aged 44. Graduate of University of California, Irvine, California College of Medicine, 1964. Licensed in California in 1965. Doctor Renshaw was a member of the Los Angeles County Medical Association.

RICE, ARTHUR H., Moraga. Died February 26, 1973 in Mexico of heart disease, aged 64. Graduate of the University of California Medical School, Berkeley-San Francisco, 1934. Licensed in Califorina in 1934. Doctor Rice was a member of the Alameda-Contra Costa Medical Association.

RITACCA, VINCENT JAMES, Glendale. Died February 23, 1973 of injuries received in a skiing accident at Snowbird Ski Resort, Utah, aged 28. Graduate of Loma Linda University School of Medicine, 1970. Licensed in California in 1971. Doctor Ritacca was an affiliate member of the Los Angeles County Medical Association.

SMOLLAR, LEO, San Diego. Died March 10, 1973 in Mission Hills of heart disease, aged 60. Graduate of the University of Illinois College of Medicine, Chicago, 1937. Licensed in California in 1938. Doctor Smollar was a member of the San Diego County Medical Society.

STEINMETZ, JOHN RICHARD, San Leandro. Died March 23, 1973 in San Francisco of heart disease, aged 63. Graduate of McGill University Faculty of Medicine, Montreal, 1937. Licensed in California in 1938. Doctor Steinmetz was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

STUEHLER, B. RICHARD, San Francisco. Died March 14, 1973 in Burlingame of heart disease, aged 59. Graduate of the Creighton University School of Medicine, Omaha, 1944. Licensed in California in 1945. Doctor Stuehler was a member of the San Francisco Medical Society.

TUTTLE, ASAPH MARSH, Bakersfield. Died October 13, 1972 in San Francisco of metastatic carcinoma, aged 84. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1915. Licensed in California in 1916. M.D. degree from California College of Medicine 1962. Doctor Tuttle was a member of the Kern County Medical Society.

VON KAENEL, WILLIAM E. San Jose. Died March 19, 1973 in San Jose of acute myocardial infarction, aged 52. Graduate of the Ohio State University College of Medicine, Columbus, 1952. Licensed in California in 1964. Doctor Von Kaenel was a member of the Santa Clara County Medical Society.

WENSLEY, CLARENCE A., Long Beach. Died January 17, 1973 in Culver City of arteriosclerotic cardiovascular disease, aged 62. Graduate of Chicago College of Osteopathy, 1945. Licensed in California in 1945. M.D. degree from California College of Medicine, 1962. Doctor Wensley was a member of the Los Angeles County Medical Association.

Refer to: Gittes RF, Bendixen HH: Pheochromocytoma—Tumor localization and surgical management. Calif Med 118: 1-6, June 1973

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Pheochromocytoma

Tumor Localization and Surgical Management

RUBEN F. GITTES, MD, *and* HENRIK H. BENDIXEN, MD, *San Diego*

Recent experience with five cases of pheochromocytoma is the basis for this report. Pharmacological blockade is to be started with phenoxybenzamine before angiographic studies. Arteriography is the preferred localization technique, particularly when combined with bone-subtraction films.

Anesthetic management requires special attention to premedication, close monitoring of cardiac rhythm, arterial and central venous pressure, and judicious administration of alpha and beta blockers. Methoxyflurane is no longer the anesthetic agent of choice because of possible nephrotoxicity.

Multiple tumors are common. Wide surgical exposure with systematic palpation of autonomic ganglia must be carried out. Manipulation of the tumor does raise arterial blood pressure in spite of adequate preoperative blockade. The alpha blockade prevents the sudden and dangerous vascular collapse which used to be seen after removal of the tumor.

RECENT EXPERIENCE with five cases of pheochromocytoma forms the basis for the present review of the clinical management of this dramatic disease. For safe, successful therapy, particular emphasis needs to be placed on (1) optimal pharmacological treatment to see the patient safely through diagnostic angiography and surgical anesthesia, and (2), the use of refined radiological techniques with thorough surgical exploration to detect multiple and extra-adrenal tumors.

From the Divisions of Urology and Anesthesia, Department of Surgery, University of California, San Diego, School of Medicine.

Submitted January 8, 1973.

Reprint requests to: R. F. Gittes, MD, Division of Urology, University Hospital of San Diego County, 225 West Dickinson Street, San Diego, Ca. 92103.

Case Summaries

CASE 1. A 41-year-old man diagnosed himself as having pheochromocytoma "again" because of a recurrence of severe headaches and perspiration eight years after the surgical removal of his left adrenal gland for a benign pheochromocytoma. Episodic hypertension was noted and catecholamine derivatives in the urine were elevated. An excretory urogram was normal.

Phenoxybenzamine (Dibenzyline®) was prescribed, 50 mg twice a day. After five days he was asymptomatic and normotensive, his hematocrit had dropped from 44 to 36 percent and angiography was deemed safe. Abdominal aortography

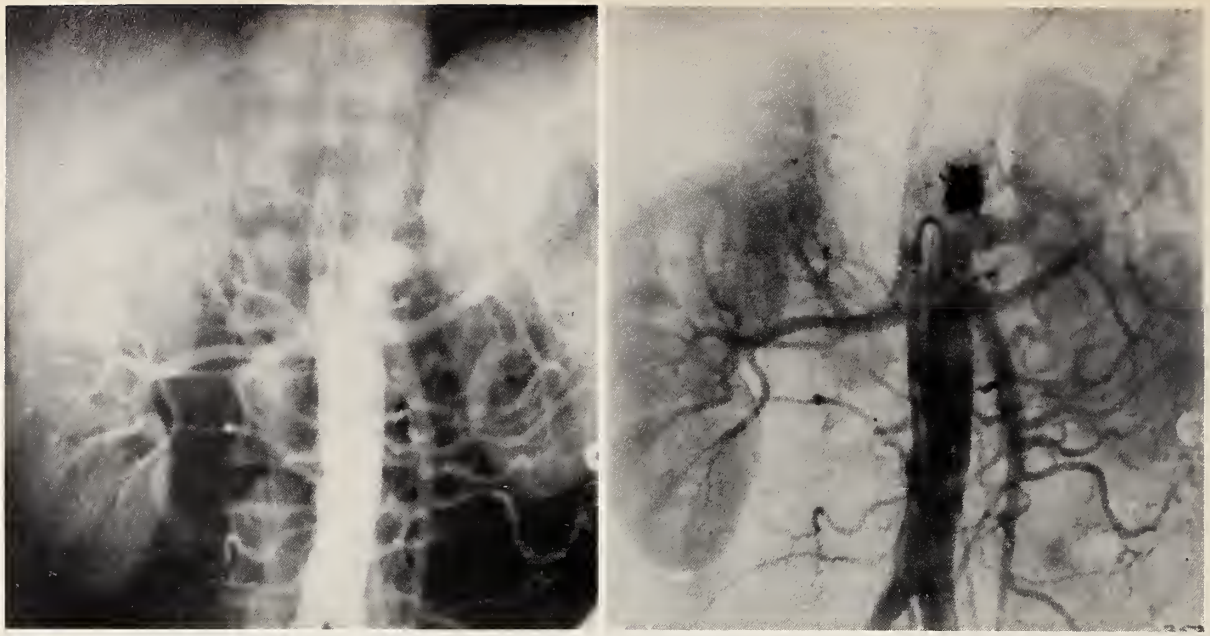


Figure 1.—Midstream aortogram in Case 1. An obvious right adrenal pheochromocytoma is seen on routine films (**left**). By use of the bone-subtraction technique (**right**), the round second tumor is seen overlying the third lumbar vertebra behind the vena cava.

as well as selective angiography at first revealed only the obvious pheochromocytoma in the right adrenal gland (Figure 1).

Phenoxybenzamine was continued for four more days, and surgical exploration then was carried out. The day before operation the patient received propranolol, 10 mg four times a day. Anesthesia was induced with thiopental sodium after premedication with 150 mg of pentobarbital and was maintained with methoxyflurane 0.3 to 1.0 percent, for a total duration of 160 minutes. Exploration included careful palpation of all autonomic ganglia along the aorta and cava. Behind the cava, at the level of the renal veins, a second tumor was palpated and dissected out. It was separate from the larger, encapsulated and benign-appearing tumor in the right adrenal gland. Histology suggested two benign pheochromocytomas, the smaller presumably arising in a sympathetic ganglion.

A review of the angiograms with the use of photographic bone-subtracting technique (Figure 1) clearly outlined the tumor blush of the second tumor, overlying the paravertebral tissue. At last report the patient was normotensive on corticoid replacement therapy.

Case 2. A 21-year-old woman with von Recklinghausen's neurofibromatosis was studied because of a consistent, non-episodic hypertension. Due to the high incidence of pheochromocytoma in patients with neurofibromatosis, determinations of urinary catecholamines and derivatives were ordered and the values were found to be elevated.

Administration of phenoxybenzamine, 10 mg every six hours, was begun. After four days the dose was increased to 20 mg every six hours. The blood pressure remained variable and averaged approximately 165/100 mm of mercury during the preoperative period.

On the third hospital day, aortography revealed a large vascular tumor in the left adrenal gland. During angiography and immediately afterward the patient complained of abdominal pain and the blood pressure rose to 200/140 mm. Phentolamine (Regitine®) was infused intravenously, and oral dibenzyline was increased to a dose of 20 mg every six hours. Operation was postponed. By the ninth day the blood pressure was relatively stable around 160/100 mm and the hematocrit had dropped from 44 to 34 percent. The patient was taken to surgery.

After premedication with Innovar®,* diphenhydramine and atropine and under thiopental sodium, curare and methoxyflurane anesthesia, the large principal tumor was removed. But, in addition, the transabdominal exploration revealed edematous enlargement of the coeliac ganglion and when it was removed and bisected a small tumor was found in the center. The blood pressure during surgical manipulation of the tumors rose as high

*A combination of fentanyl and droperidol.

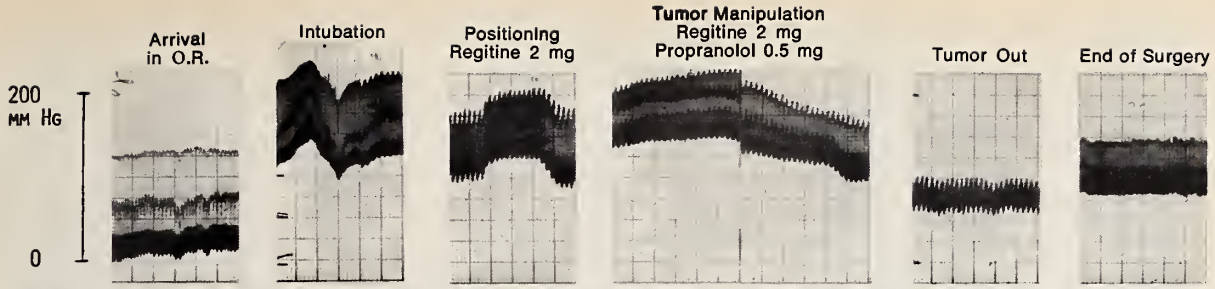


Figure 2.—Actual tracings of intra-arterial pressure monitor during course of anesthesia in Case 2. In spite of extensive preoperative blockade with phenoxybenzamine, hypertensive attacks are recorded during intubation, positioning, and tumor manipulation.

as 230/140 mm (Figure 2), requiring intermittent use of phentolamine and propranolol, in doses of 2 and 0.5 mg respectively. After the operation the blood pressure remained within normal limits.

CASE 3. A 43-year-old man with severe hypertension had positive chemical findings for pheochromocytoma. After five days on phenoxybenzamine, 20 mg every six hours, and propranolol, 10 mg every six hours, the blood pressure was variable, ranging from 200/100 to 150/80 mm of mercury, and there was a drop of only 3 percent (37 to 34 percent) in the hematocrit. The phenoxybenzamine was increased to 20 mg every four hours. Midstream aortography outlined not only a large right adrenal pheochromocytoma, but also a definite irregularity in the wall of the main right renal artery, with occlusion of several branches of the upper pole of the kidney (Figure 3). By the ninth day the hematocrit was still 34 percent, but blood pressure and pulse were stable. Surgical exploration was done under methoxyflurane anesthesia after premedication with morphine, hydroxyzine and thiopental sodium. The kidney was found mottled with large yellow areas of infarction. The tumor and kidney were resected *en bloc*. No other tumor was found.

On pathological examination a well encapsulated pheochromocytoma was found in association with an organized dissecting aneurysm of the renal artery, with occlusion of several distal branches and segmental renal infarction.

During the procedure the blood pressure ranged



Figure 3.—Association of renal artery occlusion with pheochromocytoma. The occlusion of primary branches (arrow) was noted on the preliminary midstream aortogram and was due to an established spontaneous dissecting aneurysm of the main renal artery. The large pheochromocytoma is shown in detail in a selective angiogram of the right middle adrenal artery.

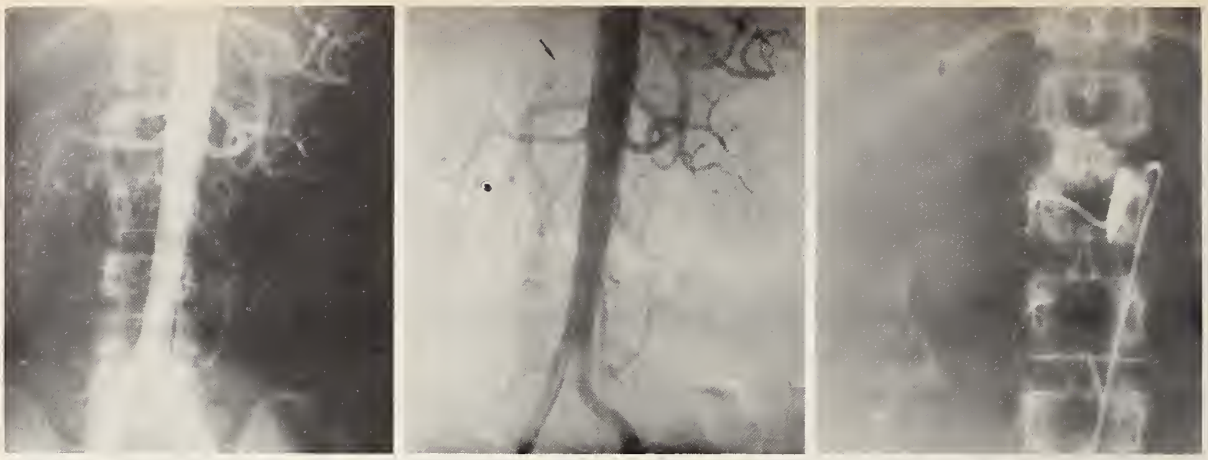


Figure 4.—Angiography with bone-subtraction demonstrates a pheochromocytoma of the right coeliac ganglion. The tumor masked by the first lumbar vertebra in the standard film (left) is only seen after the immediately performed bone subtraction (center, arrow) and is then further defined by the selective arteriogram of the lumbar artery (right).

between 230/130 and 70/40 mm of mercury. The duration of anesthesia was 4.20 hours, with methoxyflurane concentrations ranging from 0.2 to 1.5 percent.

Postoperatively the patient had evidence suggestive of high output renal failure, with 24-hour urine volumes between 1,200 and 4,650 ml and serum creatinine climbing to a maximum of 5.4 mg on day five. Urine oxalate on the eighth postoperative day was normal. The patient remained normotensive and the creatinine slowly decreased to 2.9 mg at 14 days and to 1.3 by the 38th day.

Case 4. Continuous significant hypertension was the only symptom which prompted the physician of a 50-year-old woman to perform a diagnostic phentolamine (Regitine®) test—and it was positive. Urine tests confirmed the diagnosis of pheochromocytoma. After 12 days on phenoxybenzamine, 40 to 60 mg per day, the hematocrit dropped from 46 to 43 percent and the blood pressure ranged from 180/100 to 145/80 mm of mercury. Then angiography was done, and no tumor blush was seen in the routine films (Figure 4). But immediate bone-subtraction films (Figure 4 *center*) did show a 2 cm tumor overlying the body of the first lumbar vertebra; then selective angiography (Figure 4 *right*) outlined the tumor in the area of the coeliac ganglion.

Exploration one day later, after continued alpha adrenergic blockade, led to the removal of the coeliac ganglion, the body of which was found to be supplanted by a typical pheochromocytoma. No other tumors were found.

Anesthesia was induced with thiopental sodium and maintained with nitrous oxide, meperidine and curare. During the procedure phentolamine, 5 mg, was needed intermittently to control the blood pressure. After the operation the blood pressure remained within normal range.

Case 5. A 39-year-old woman was treated for hypertension accompanied by severe epistaxis, headaches, increased nervousness, tachycardia, palpitations and syncope. The blood pressure had recently been measured at 260/160 mm of mercury. The patient was transferred to University Hospital of San Diego County from another hospital one day after aortography had demonstrated a 6x9 cm right suprarenal mass. Urinary catecholamines, vanillylmandelic acid and metanephrines were decidedly elevated.

The patient's blood pressure was 240/140 mm at the time of admission, and a phentolamine infusion was used for immediate control. Administration of phenoxybenzamine, 10 mg every six hours was begun. Four days later the dose was increased to 20 mg every six hours; after another day to 30 mg every six hours; and after two more days to 40 mg every six hours. The total period of pretreatment was 14 days, during the last seven of which the patient also received propranolol, 10 mg every six hours.

It was not until the last two days preoperatively that the blood pressure was fairly stable at approximately 170/105 mm of mercury. The hematocrit had dropped from 41 to 36 percent.

Two weeks following admission the patient was premedicated with morphine and hydroxyzine; anesthesia was induced with thiopental sodium

and maintained with N_2O, curare and methoxyflurane. Resection of the pheochromocytoma was carried out. No other tumors were found. The blood pressure remained well controlled throughout, in the range of 160/90 to 120/70 mm. No phentolamine or propranolol was needed. The postoperative course was without circulatory problems and the blood pressure was within normal range thereafter.

Pharmacological Management

Recent advances in the use of adrenergic blockers make possible the prevention of some, but not all, of the dramatic swings in blood pressure during surgical treatment of pheochromocytoma.[1-5] Certainly eliminated by adequate preangiographic and preoperative adrenergic block is the lability of blood pressure under minor stress. Also eliminated is the occurrence of the profound hypotension that otherwise ordinarily follows removal of the tumor. Most fatalities from pheochromocytoma in the past were associated with the late and profound hypotension, not with the earlier hypertensive crises.[6]

The principal effect of pretreatment with alpha adrenergic blocking drugs such as phenoxybenzamine may well be the elimination of sustained vasoconstriction and the restoration of normal volume of circulating blood. A fall in hematocrit in the absence of blood loss to explain it, warns of the expansion of the contracted vascular bed in time to avoid sudden vascular collapse at the time of removal of the tumor. Elective transfusion may be required preoperatively if the hematocrit drops below 35 percent.

Pretreatment with adrenergic blocking drugs also lowers the blood pressure and gives the patient symptomatic relief from headache, palpitations, nausea, anxiety and sweating. Phenoxybenzamine is the preferred agent, as it is long-acting and is given by mouth. Commonly, too small doses are used. The effective dose is 1.0 to 2.0 mg per kg of body weight per 24 hours, divided into three or four doses. Side effects are the characteristic nasal congestion and orthostatic hypotension. When phenoxybenzamine treatment is started, the patient should be confined to bed until normal blood pressures are achieved along with a drop in hematocrit of about 5 percent. Fear of orthostatic hypotension must not lead to undertreatment.

Pretreatment also with beta adrenergic blocking agents, such as propranolol, has been advocated. Because of the relatively short action of these drugs, they cannot sustain protection, nor are they strongly indicated except in the face of persistent arrhythmias or sinus tachycardia exceeding 120 beats per minute. Methyl tyrosine, an inhibitor of the enzyme tyrosine hydroxylase, has been advocated for chronic management of pheochromocytoma,[1] but it can be toxic.[4] We have not used it. The majority of patients are adequately pretreated with phenoxybenzamine alone.

Premedication before operation is of special importance to reduce anxiety and the accompanying high blood pressure. The premedication of choice is pentobarbital sodium, which will obtund cortical arousal and reticular activation.

For the same reasons, thiopental sodium is the induction agent of choice. Succinylcholine is used for intubation after a small dose of curare to avoid fasciculations. Much has been written about the choice of agents for maintenance of anesthesia.[1,2,4] There is general agreement that cyclopropane should be avoided; but diethyl ether, halothane, methoxyflurane and N_2O-relaxant-narcotic combinations have been used successfully. Methoxyflurane enjoyed special favor for a time, but in our opinion the potential nephrotoxicity has recently taken it out of contention.[14] We used methoxyflurane in four of our five cases. In one of the cases herein reported (Case 3) the combination of oliguria in the immediate postoperative period followed by high urine outputs associated with rising values of serum creatinine could have represented the high-output renal failure associated with this anesthetic.

During operation, indwelling catheters permit continuous recordings of arterial and central venous pressures. In addition, the electrocardiogram is displayed on an oscilloscope and the body temperature is measured. Such close monitoring provides precise data for patient management and gives early warning of any deleterious trend. All patients receive controlled ventilation, guided by the arterial blood gas measurements.

Despite adequate pretreatment, hypertensive episodes may be expected when the patient is moved, or on endotracheal intubation, or while the abdomen is being prepared; and especially such episodes are associated with retraction or manipulation of the tumor. The short-acting alpha-blocking agent, phentolamine, is used in intermittent doses of 1 to 5 mg to blunt the hypertensive peaks. Persistent arrhythmia or tachycardia is treated with propranolol in intermittent doses of

0.5 to 1.0 mg. While norepinephrine is kept in readiness, the first treatment of the falling blood pressure after tumor removal should be volume replacement. Only rarely should norepinephrine be required at this time, provided adequate blood volume has been maintained.

Radiological and Surgical Exploration

We have learned to depend heavily on preoperative angiographic localization[7] rather than plasma catecholamine levels[8] or surgical exploration alone.[4] Aortography and selective angiography must be undertaken only after adrenergic blockade is established, and even then intravenous phentolamine and propanolol must be at hand and the pressure and pulse closely monitored.

Immediate bone-subtraction films should be processed after the initial midstream aortogram. Two of the patients here reported upon had tumors seen only with this technique (Figures 1 and 4). A suspicious blush is then defined further by selective angiography, as in the coeliac ganglion tumor in Case 4. Multiple tumors may be anticipated in 15 percent of adults,[4] and therefore the angiograms must be scrutinized for a second tumor even when an obvious tumor is seen. Multiplicity or bilaterality is particularly common in patients with familial neuroectodermal disease such as neurofibromatosis[9] or familial pheochromocytoma associated with medullary carcinoma of the thyroid.[10]

Close attention to the kidney vessels on the angiograms is suggested by the association of renal artery stenosis and pheochromocytoma,[11] illustrated in Case 3. The size of the tumor is often such that it involves the branches of the renal artery, and part or all of the kidney may be sacrificed.[12] For these reasons, the surgeons must have familiarity with renal surgery, and the condition of the opposite kidney must be determined beforehand.

Meticulous and systematic transabdominal exploration is still required in spite of the angiographic advances such as bone-subtraction films and selected angiograms. Careful palpation of the vena cava, coeliac and hypogastric plexus, and both sympathetic chains may reveal an unsuspected second tumor, as in Cases 1 and 2 herein. When a large tumor is present (Cases 2, 3, 5) a thoraco-abdominal incision is preferred for optimal exposure and vascular control of the adrenal area.

Postoperatively the monitoring with intra-arterial and central venous catheters is to be maintained at least 24 hours. The well-managed patient with adequate vascular volume will not have hypotension unless it is cardiogenic.[4,13] Postoperative hypertension might suggest residual tumor or renovascular damage,[12] and these possibilities are sorted out by repeated determinations of urinary catecholamines and plasma renin values, and by further arteriography if necessary.

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Evolution of the Acid-Base Status in Cardiac Arrest

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In a study of the evolution of acid-base status in 26 patients who had cardiopulmonary arrest in the operating room, it appeared that:

The determination of acid-base status within the first hour post-cardiac arrest is useful in differentiating final survivors from non-survivors.

Respiratory or combined acidosis carries a poor prognosis not evidenced for metabolic acidosis.

Late respiratory complications are more frequent in patients with initial combined acidosis.

Treatment should be instituted on the basis of frequent determinations of acid-base status, since accurate diagnosis of degree and type of acidosis cannot be done on clinical grounds only.

Recovery of consciousness is influenced by the type and severity of acidosis, less so by duration of arrest; and that high pCO_2 is associated frequently with unconsciousness after recovery of circulatory function.

SINCE THE INTRODUCTION and wide utilization of external and internal cardiopulmonary resuscitation techniques, there have been numerous reports on diverse factors related to their effectiveness. However, there are few reports concerning the acid-base balance in this emergency, and some of them give contradictory evidence regarding its possible prognostic value.

Our experience with 26 patients who had cardiopulmonary arrest while being submitted to surgical interventions in the Vargas Hospital of Caracas, and in whom treatment was begun without appreciable delay, will be presented here. We shall emphasize our findings on the acid-base balance and its relation to survival rates, cerebral damage, and duration of arrest, in order to establish whether there is any prognostic value in serial determinations of acid-base status besides their well-established value as a guide for treatment, and in the assessment of the actual condition of the patient.

Material and Methods

From 40 instances of cardiopulmonary arrest observed during three years in the Vargas Hospital and reported elsewhere,[1] 26 were selected to be reported here because serial determinations of arterial acid-base status had been carried out, beginning shortly after the diagnosis of arrest and then continuing for 24 to 48 hours.

Twenty-four of the accidents happened in the operating room and two in the cardiac catheterization laboratory. In both places, what with instrumental facilities, the presence of trained medical and paramedical personnel and the continuous monitoring, the arrest was recognized and treated without delay, and acid-base determinations were made within an hour of the beginning of arrest. In most cases, these determinations were made within ten minutes.

Cardiac arrest was defined as "a sudden and unexpected loss of pulse and arterial pressure"[2-4]; recovery was defined as "the conversion of ineffectual or absent cardiac action to effectual cardiac action, no longer requiring external or internal cardiac compression." The complete re-

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covery of neurological function was not applied to defining immediate success,[3] but its absence was taken as an indication of cerebral damage.

All 26 cases met the definition of temporary success of cardiopulmonary resuscitation, since all the patients were temporary survivors. In the rest of the report, the term *survivors* is applied to patients who left the hospital alive after a variable time of recovery.

The duration of arrest was computed as the duration of the resuscitation maneuvers, since the area in which the arrest occurred permitted diagnosis to be made without delay and the maneuvers were continued until recovery was achieved.

The acid-base data were obtained from 82 arterial blood specimens collected anaerobically at frequent and variable intervals shortly after the beginning of arrest, during the resuscitation maneuvers, and throughout the following 24 to 48 hours. Each specimen was analyzed immediately in duplicate, utilizing an Astrup AME 1-C (Radiometer) equipped with a glass electrode for pH determinations. Partial pressure of CO_2 (pCO_2) and base excess (BE) or base deficit (BD) were calculated, using the nomogram of Siggaard-Andersen, after the arterial blood was equilibrated with two different gas mixtures of known concentration.[5,6]

The classification of the acid-base alterations was based on the nomenclature accorded by the Ad Hoc committee of the New York Academy of Science in 1964.[7] Our normal values after correction for the hemoglobin concentration were: pH = 7.36-7.42, pCO_2 = 35-45 mm of mercury, and BE (base excess) +2 to −2 mEq per liter.

The management of the arrest was the responsibility of the medical team present at the time of the intervention. The method of treatment consisted of artificial ventilation via endotracheal intubation, external massage followed by internal compression when the first was not effective, or when the chest was already opened; electrical defibrillation when indicated, catecholamines (norepinephrine, isoproterenol), lidocaine, and other antiarrhythmic drugs; fluids and blood when indicated. Sodium bicarbonate was administered, utilizing as a guide the formula of Astrup and Mellemgaard[5] for calculation of the bicarbonate deficit corrected for the hemoglobin value and body weight. Usually, 50 mEq of 5 percent sodium bicarbonate was administered before the acid-base results were available but after the first specimen

TABLE 1.—*Clinical Summary of 26 Cases of Cardio-Pulmonary Arrest in the Operating Room*

Case No.	Age	Sex	Procedure	ECG at beginning of arrest	Duration of arrest	Consciousness post-arrest	Outcome
1.	48	F	Inguinal hernioplasty	V. fib.	15	Unconscious	Died—16 hr
2.	70	F	Exploratory laparotomy	N.D.	15	Unconscious	*Died— 6 hr
3.	80	F	Enucleation—right eye	Bradycardia, asystole	30	Conscious	Died—19 days
4.	33	F	Left internal carotid artery aneurysm resection	N.D.	15	Unconscious	Died—1½ hr
5.	26	M	Surgical correction of micrognathia	Asystole	18	Unconscious	Died—42 hr
6.	59	F	Sigmoid colon polypectomy	V. fib.	7	Conscious	Died— 5 days
7.	14	M	Cardiac catheterization	V. fib.	60	Conscious	Died—21 hr
8.	34	F	Mitral valve commisurotomy	Asystole	10	Conscious	Died— 5 days
9.	16	F	Exploratory laparotomy	N.D.	15	Unconscious	Died—31 hr
10.	85	M	Partial gastrectomy	N.D.	65	Unconscious	Died—1½ hr
11.	56	F	Abdomino-perineal resection	N.D.	9	Unconscious	Died—18 hr
12.	48	F	Total thyroidectomy	Asystole	10	Unconscious	Died—30 hr
13.	67	M	Femoro-popliteal bypass	Asystole	15	Unconscious	Died— 6 days
14.	60	M	Partial gastrectomy	Asystole	55	Unconscious	Died— 2 hr
15.	30	F	Hysterectomy	Asystole	50	Unconscious	Died— 2 hr
16.	28	F	Hysterectomy	V. fib.	15	Unconscious	Died— 2 hr
17.	53	M	Right radial neck dissection	N.D.	60	Unconscious	†Discharged—14 days
18.	78	M	Abdominal aorta bypass graft	V. fib.	50	Conscious	Discharged—30 days
19.	25	M	Brain tumor resection	N.D.	25	Unconscious	†Discharged—13 days
20.	68	M	Cholecystectomy	N.D.	7	Conscious	‡Discharged—15 days
21.	67	M	Right internal carotid artery aneurysm resection	N.D.	8	Conscious	‡Discharged—15 days
22.	8	M	Cardiac catheterization	V. fib.	1	Conscious	Discharged—48 hr
23.	56	F	Abdomino-perineal resection	Asystole	4	Conscious	Discharged—17 days
24.	60	M	Aorto-iliac bypass	Asystole	7	Conscious	‡Discharged—30 days
25.	17	M	Ulnar nerve neurorrhaphy	V. fib.	3	Conscious	‡Discharged—14 days
26.	55	F	Abdomino-perineal resection	N.D.	5	Conscious	Discharged—30 days

Abbreviations: V. fib. = ventricular fibrillation; N.D. = not documented.

*Mild preop acidosis corrected. †Unconscious. ‡Returned to work.

was collected. Standard statistical techniques, such as contingency analysis, Student t test and linear correlation curves, were applied in order to assess the statistical significance of the data.

Results

Table 1 summarizes the clinical information on these patients. There was no difference in age or sex distribution between the survivor and the non-survivor groups. The overall age range was from 8 to 85 years, with a mean of 49 years. Half of the patients were females, but 11 of the 16 non-survivors were females and 8 of the 10 survivors were males.

Preoperative clinical and paraclinical tests showed 80 percent of the patients to have cardiovascular or pulmonary diseases, manifested as arteriosclerotic heart disease, rheumatic heart disease, chronic bronchitis, or emphysema.

Only six of the interventions were performed in emergency; all others were done as elective procedures. In two other instances, the arrest occurred while the patients were undergoing cardiac catheterization before a surgical procedure.

Of the 26 patients, 16 died after successful resuscitation and before being discharged from the hospital. Ten left the hospital alive and were considered survivors; however, two of these ten were transferred to a convalescent hospital because of severe neurological damage, without recovery of consciousness.

Evolution of acid-base status in survivors and non-survivors after cardiac arrest. In order to delineate differences in acid-base evolution, these patients were classified retrospectively into two groups. Group A consisted of ten patients who were discharged alive and considered as survivors; Group B consisted of 16 patients who died of complications resulting from their cardiac arrest before they were discharged.

Chart 1 shows a plotting of the acid-base results in these two groups, as taken sequentially during the first 48 hours post-arrest.

All 26 patients survived the first hour; specimens of blood taken during this period disclosed the "final" survivors to have normal or close to normal acid-base status ($pH = 7.40 \pm 0.03$; $CO_2 = 34.9 \pm 3.8$ mm of mercury; BE $= 1.78 \pm 3.1$ mEq per liter). There was a statistically significant difference with the non-survivors, who had a severe combined acidosis ($pH = 7.1 \pm 0.08$, $pCO_2 = 63.2 \pm 11.7$, BE $= -10.8 \pm 2.7$).

Six patients died during the following five hours.

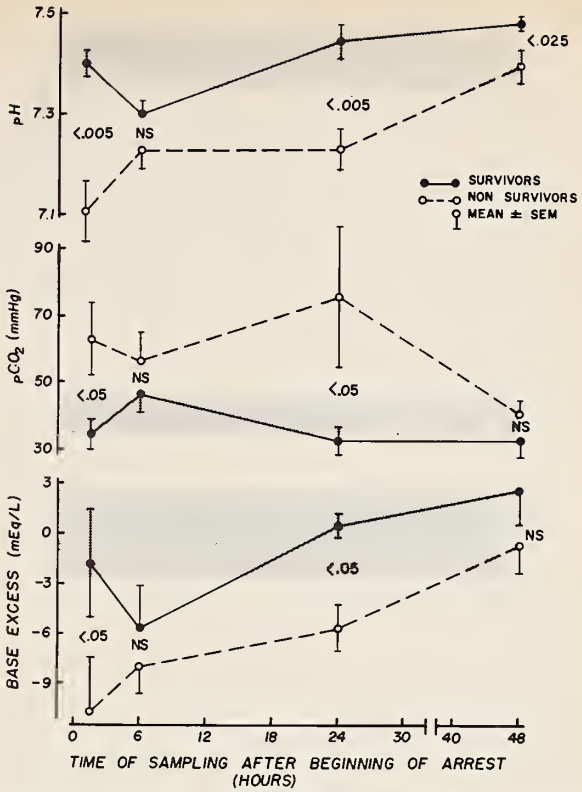


Chart 1.—Evolution of acid-base status in survivors and non-survivors after cardiac arrest. The non-survivor group showed a severe combined acidosis in the first sample post-arrest, and a further worsening of respiration in the next 18 hours. In contrast, the survivor group had a moderate metabolic acidosis initially, with fast restoration of normal acid-base status.

By this time, the survivor group had a moderate metabolic acidosis ($pH = 7.31 \pm 0.03$, $pCO_2 = 46 \pm 5$ mm of mercury; BE $= -5.8 \pm 2$. mEq per liter), while the remaining non-survivors had improved their combined acidosis ($pH = 7.23 \pm 0.04$; $pCO_2 = 56.9 \pm 8.4$ mm of mercury; BE $= -7.9 \pm 1.6$ mEq per liter).

During the next 18 hours, two more patients died. After readministration of bicarbonate, the survivors returned to a normal acid-base status ($pH = 7.44 \pm 0.04$; $pCO_2 = 32.2 \pm 4$ mm of mercury; BE $= -0.8 \pm 1.5$ mEq per liter), showing a trend toward respiratory alkalosis due to slight hyperventilation. In the non-survivor group the metabolic derangement improved, as shown by a decrease in the base deficit, but many of them had a worsening of ventilation caused by previous gastric aspiration pneumonitis, pulmonary infections and atelectasis ($pH = 7.22 \pm 0.03$, $pCO_2 = 76 \pm 21$ mm of mercury; BE $= -5.3 \pm 2.1$ mEq per liter). These differences in acid-base status were again statistically significant.

TABLE 2.—*Relation of Duration of Cardiac Arrest to Acid-Base Status,* Survival Rate, and Recovery of Consciousness*

	Duration of arrest	
	10 minutes or less	*More than 10 minutes*
No. of patients	11	15
pH	7.39±0.03	7.12±0.07†
pCO_2 mmHg	37.6±5.4	61.4±11.4‡
Base excess (BE) mEq/L	3.2±1.4	−10.8±2.8‡
Survival rate (percent)	63.6	20†
Recovery of consciousness (percent)	91	20†

Results are given as mean ± SEM.

*As determined in the first sample taken after cardiac arrest.
†$p<0.005$
‡$p<0.05$

Vigorous supportive treatment was instituted in the following hours, but four patients died the next day. The survivor group showed a slight combined alkalosis at 48 hours post-arrest (pH = 7.48 ±0.01, pCO_2 = 33.2±4 mm of mercury; BE = 2.5 ±0.6 mEq per liter). The four remaining patients in the non-survivor group were returned to normal acid-base status for the first time after cardiac arrest (pH = 7.39±0.02, pCO_2 = 41.2±7 mm of mercury; BE = 0.57±1.2 mEq per liter). These patients died later of pulmonary complications subsequent to the cardiac arrest, two on the fifth day, one on the sixth day, and one on the nineteenth day.

Duration of arrest. In Table 2, the acid-base status determined during the first hour after cardiac arrest, the survival rate, and recovery of consciousness, are analyzed as a function of the duration of arrest, considering 10 minutes as an empirical discriminating time factor.

When an effective cardiac action was restored in less than 10 minutes, the acid-base status was slightly altered, survival rate was more than 60 percent and almost every patient regained consciousness. On the other hand, if arrest could not be reversed in that period of time, acid-base status showed a severe combined acidosis, survival rate was 20 percent, and only one out of every five patients regained consciousness. These differences were statistically significant ($p<0.05$).

An attempt was made in 18 patients to correlate their acid-base status at the end of the resuscitation maneuvers to the duration of arrest (Chart 2). Patients with alkalosis, or those in whom arrest lasted longer than 20 minutes, were excluded. A significant inverse correlation ($r=-0.66$, $p<0.02$) was obtained for pH and base excess, but it was not significant for pCO_2. This would indicate that the metabolic factor of the acidosis increases with longer periods of arrest, but the effect of treatment on these values precludes statement of any valid conclusion.

Recovery of consciousness. The status of consciousness was evaluated in every patient immediately after cardiovascular function resumed. As can be seen in Table 3, patients who remained unconscious after recovering from cardiac arrest had a severe combined acidosis in the specimens taken during the period of arrest, or in the first hour afterward (pH = 7.04±0.05, pCO_2 = 71.2± mm of mercury; BE = −13.4±3 mEq per liter).

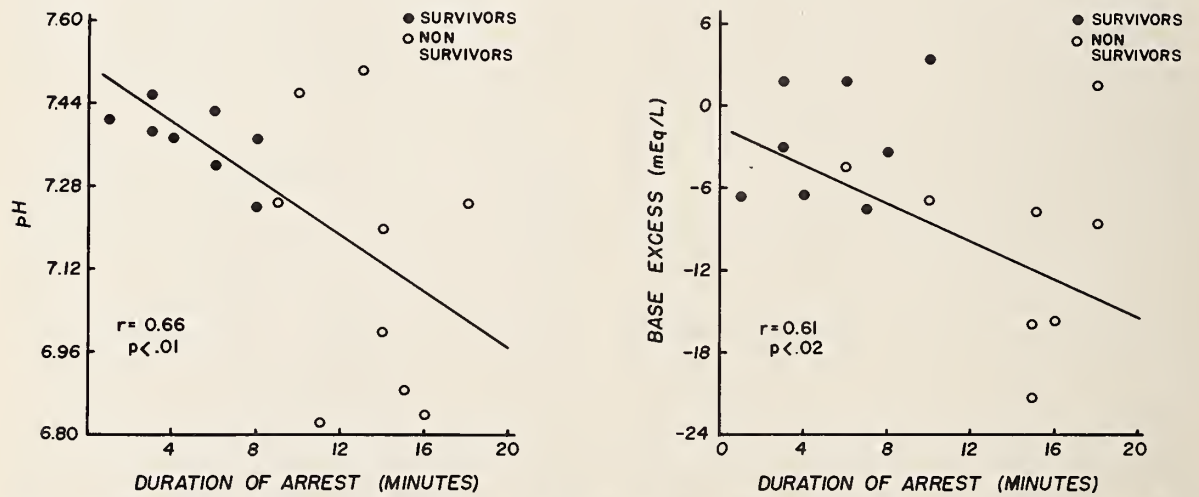


Chart 2.—Relationship of duration of arrest to pH and base excess values determined within one hour post-arrest. The metabolic factors of the acidosis post-cardiac arrest tend to increase significantly with longer duration of the arrest. The wide scattering of individual values indicates a high degree of variability due to influence of the treatment and the respiratory status on these parameters.

By retrospective analysis their survival rate was only 14.2 percent. In contrast, patients who regained consciousness had a normal acid-base status, coupled with a survival rate of 66.6 percent. Duration of arrest was longer in patients who did not regain consciousness (35±12 minutes) than in those who did (15±8 minutes)—($p>0.01$). This difference was not statistically significant.

Type of acidosis. In the first blood specimen withdrawn, three patients showed normal acid-base status, three showed either respiratory (two) or metabolic (one) alkalosis, and the remaining 20 patients showed acidosis. Normal values were seen when the arrest lasted less than four minutes. The three instances of alkalosis were felt to be the consequence of either too vigorous pre-arrest or intra-arrest artifical ventilation, or an excessive amount of bicarbonate administered.

Of the 20 acidotic patients (Table 4), nine had predominant metabolic acidosis and 11 combined acidosis. A much poorer prognosis was associated with the presence of combined acidosis, since it was related to a survival rate of 11.1 percent. Patients with metabolic acidosis had a survival rate of 60 percent. All three patients with normal acid-base status were final survivors, but with alkalosis the outcome was variable.

Discussion

One must distinguish cardiac arrest as a terminal event in a serious systemic disease from arrest occurring to a less seriously ill person during diagnostic (catheterization) or therapeutic (anesthesia, surgical operation) procedures. Most of the former will not survive arrest; most of the latter (40 to 90 percent) will recover initially if the precipitating factor causing the arrest can be removed. However, a very high proportion of these patients die shortly thereafter of complications of their cardiac arrest,[2-4,8,9] leaving only 5 to 30 percent as final survivors. In this group, then, it is essential to recognize prognostic indices which allow prevention of early and late mortality.

From our data, it is evident that the determination of acid-base status, when made within the first hour post-arrest, has prognostic value in delineating the survival possibilities of individual patients. The survivors had normal or close to normal acid-base status, as compared with a severe combined acidosis seen among the non-survivors, particularly in the presence of hypercapnia. These findings of severe acidosis in non-survivors after cardiac arrest have been reported previously.[10-12]

TABLE 3.—*Relation of Recovery of Consciousness* to Acid-Base Status†*

	Conscious	*Unconscious*	*p*
pH	7.38±0.04	7.04±0.05	<0.001
pCO_2 mmHg	36.5±5	71.2±14	<0.05
BE mEq/L	−4.0±2	−13.0±3	<0.025
Survival rate (percent)	66.6	14.2	<0.005
Duration of arrest (minutes)	15±8	35±12	N.S.

Results are given as mean ± SEM

*As determined after recovery of cardiac function.
†Samples during the first hour post-arrest.

TABLE 4.—*Survival Rates in Acidosis Post-Cardiorespiratory Arrest*

Type of acidosis	*Survival rates*
Metabolic	60
Combined	11.1
p	<0.005

Jude and coworkers[2] found significant differences in the severity of base deficit between survivors and non-survivors after cardiac arrest in the operating room. However, in contrast with our results, neither pH nor pCO_2 determined simultaneously were significantly different.

Subsequent specimens reflected the effects of the treatment. The slight metabolic acidosis observed in the survivors during the six hours after arrest can be explained by increased levels of lactic acid and other acidotic metabolities washed out from ischemic peripheral capillary beds, once circulation is re-established.[13] The CO_2 produced by the buffering action of the blood might have induced a slight increase in pCO_2. Since in these patients there was little deviation from the normal A-B pattern in the first speciman, bicarbonate was not administered in large amounts, allowing the acidosis to be evident. At this stage, the appearance of metabolic acidosis did not alter prognosis. On the other hand, large amounts of bicarbonate and appropriate assisted ventilation were given accordingly to the non-survivors, thus substantially improving their acid-base balance.

Before the end of the first 24 hours post-arrest, there was a worsening of ventilatory function in many non-survivors, although they were maintained under positive-pressure artificial ventilation and close surveillance. This worsening was the result of aspiration of gastric fluids, atelectasis, broncho-pneumonias, and sudden interruption of artificial ventilation due to dislodgement or replacement of intratracheal tubes.

It is important to note that patients with high pCO_2 at the periarrest period were more prone

to those respiratory complications, which were frequently fatal. By contrast, survivors returned to normal A-B status during the first 24 hours.

As is well established in previous reports,[2,4,14,15] the duration of arrest influenced prognosis. Patients whose arrest lasted less than 10 minutes had 60 percent survival rate, as compared with less than 20 percent when arrest lasted longer than 10 minutes. The longer duration of arrest was accompanied by severe combined acidosis and late recovery of consciousness, as could be expected from the more severe degree of tissue hypoxia and cerebral edema.

A good correlation between buildup of metabolic acidosis and duration of arrest has been demonstrated experimentally[16] and also reported in some clinical studies.[17] This correlation permitted the development of formulae for calculation of bicarbonate dosage, based on duration of arrest and body weight. In our series, although there was a significant degree of correlation between duration of arrest and pH or base deficit (Chart 2), it was not accurate enough for development and application of such formulae. The status of ventilation before and during arrest modified the effects of duration of arrest on the acid-base status, precluding the application of formulae not based on the actual pH, pCO_2 and BE of blood for administration of bicarbonate.

Regarding predisposing factors, Camarata et al[8] recently found acidosis preceding cardiac arrest in a high proportion of critically ill patients. When no preceding acidosis was present, an acute anoxic period was directly related to the arrest. Our patients did not have a critical condition as a cause of acidosis, but the large incidence of combined acidosis in the first speciman suggests that hypoxemia and hypercapnia during the surgical procedure were major causes of arrest, and determinants of late survival rate.

The recovery of consciousness, as mentioned before, was late, if ever present, in the acidotic patients, who also had longer duration of arrest and poor survival rate (Table 3). Particularly high pCO_2 was related to long periods of unconsciousness and cerebral damage. Hypoxia and hypercapnia cause cerebral vasodilation and subsequent cerebral edema[14,18] expressed clinically as unconsciousness. The fact that arrest lasted longer, although it was not statistically significant in unconscious patients, suggests that other variables such as the degree of acidosis and pCO_2 retention were greater influences on the recovery of consciousness.

We observed a very low survival rate in cases of combined acidosis (11 percent) as compared with cases of metabolic acidosis (60 percent), a fact which corroborates the findings of Chazan el al[11] and gives this early finding an ominous prognostic value after cardiac arrest.

Some observations regarding treatment are pertinent. Since it was not possible to predict the type and severity of acidosis on clinical grounds, no formula for administration of bicarbonate based solely on duration of arrest and body weight could be developed. Thus, the actual determination of the acid-base status is essential for guiding and evaluating therapy.[2,11,14]

Ventilatory failure was frequently associated with death; therefore, every effort should be aimed at ensuring good ventilation as early as possible. This will also facilitate the treatment of metabolic acidosis in such cases by eliminating the excess of CO_2 produced by the buffering action of bicarbonate, and improving oxygenation.[12,13] Close surveillance and preventive measures must be taken to avoid late respiratory failure.

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Cancer of the Vulva

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In the past three decades a number of reports have confirmed that radical vulvectomy with inguinal lymphadenectomy is the appropriate treatment for invasive carcinoma of the vulva.[1-4] Pelvic lymphadenectomy has been utilized by some surgeons, but for the most part only in selected cases. As with other gynecologic malignant diseases, individualization of treatment has resulted in the best overall results considering both the intention of cure and the quality of life. Neoplasms occurring on the vulva differ quite distinctly in malignant potential from skin cancers arising elsewhere in the body. Treatment therefore must be more aggressive. The treatment plan can only bring success if it is based on a logical approach that is designed to eradicate the disease locally and in its predictable sites of spread.

Histological Considerations

Accepting that malignant neoplasms of the vulva are not uniform histologically and that fine pathological distinctions are often difficult, we shall consider them in four categories.

1. Squamous cell carcinoma
2. Melanoma
3. Sarcoma
4. Adenocarcinoma

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Invasive Squamous Carcinoma

Invasive squamous carcinoma of the vulva comprises 90 to 95 percent of all malignant lesions of the vulvae. It is predominantly a disease of postmenopausal women. The average age at diagnosis is 65. While the majority of cases seem to arise on an otherwise healthy vulva, any chronic disturbance of the vulva, including granulomatous disease, condyloma accuminata and the vulvar dystrophies, predispose to squamous carcinoma.

Procrastination by the patient or want of suspicion by the physician may delay diagnosis. Fortunately vulvar carcinoma tends to grow slowly and remain confined to the vulva for relatively long periods. The most common presenting complaints are vulvar pruritis, bleeding, burning, pain and the discovery of "a growth" by the patient.

Diagnosis can be made only by physical examination and liberal use of tissue biopsy. The lesions may assume a great variety of morphologic characteristics, including exophytic and papillary or endophytic and ulcerative. When carcinoma develops on the background of chonic vulvar disease, no well-demarcated lesion suspicious of invasive cancer may be present and multiple biopsy of hypertrophic, ulcerated, fissured and other irregular areas must be carried out to make the diagnosis of malignant neoplasia or exclude it.

Although the primary lesion may appear any-

where on the vulva, certain sites are more commonly involved. Approximately 70 percent of the lesions occur on the labia, three times as often in the majora than in the minora. Next in frequency is the clitoris, which is involved in roughly 13 percent of the cases. The urethra and the perineal body can also be primary sites.

Management

The rational management of any malignant disease must be based upon knowledge of its spread characteristics and the applicability and efficacy of the available means of treatment. Vulvar carcinoma spreads almost exclusively by local invasion and lymphatic metastasis. Hematogenous dissemination is distinctly unusual.

The lymphatic channels of the vulva from the hymenal ring, posterior fourchette and perineal body drain outward to the labial-crural fold and upward via the labia majora and minora to the mons veneris. The lymphatic trunks turn abruptly lateral in the superior portion of the mons, terminating in the superficial nodes of the groin. Decussation of the lymphatic drainage does occur in the mons, providing a pathway for contralateral groin metastasis.[15]

The orderly lymphatic flow proceeds from the superficial (femoral and inguinal) groin nodes to the deep groin nodes located beneath the cribriform fascia in the femoral triangle and intimately associated with the femoral vessels. These deep inguinal and femoral nodes in turn drain to the pelvic wall nodes around the iliac vessels and thence up the retroperitoneal chain.

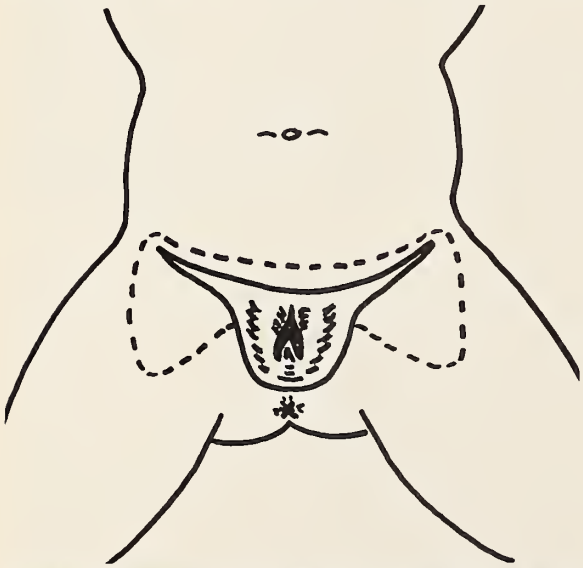


Figure 1.—Diagram of vulvectomy incision. The solid line represents the limits of the skin incision and the dotted line the extent of undermining.

The clitoris (but not the clitoral prepuce), urethral meatus and possibly Bartholin's gland have lymphatic channels which proceed to the pelvic wall directly, although these structures are also supplied with channels which drain into the groin. Local extension of vulvar carcinoma may involve the anus, vagina or rectum, all of which have lymphatic drainage direct to the pelvic wall.

Modern surgical treatment of carcinoma of the vulva has evolved from the work of Taussig,[2] and Way.[3,4] Under the influence of Taussig, Dr. Stanley Way was stimulated to embark on his extensive and fruitful clinical experiment with this disease in the late 1940's. With a team approach and a consistent treatment plan, he managed 146 patients with carcinoma of the vulva by radical surgical operation. He reported a five-year survival rate of 74 percent for all stages, which was clearly superior to that associated with radiation therapy or vulvectomy, which was the standard treatment at that time. The validity of Way's experience has been repeatedly confirmed by other investigators.[13,14,16,17]

Surgical extirpation is now the main and accepted therapy for this lesion.[18] Important points relevant to radical operation concern (1) the removal of the mons veneris, (2) excision of a sufficiently wide margin around the tumor, (3) dissection to an adequate depth with removal of all tissues superficial to the urogenital diaphragm, and (4) resection of neighboring structures such as urethra, vagina, anus or even bone if the tumor has reached these sites. The extent of the vulvectomy can be logically supported by reference to the course of the collecting lymphatic channels and the frequency with which multi-focal lesions are found in this disease. Dissection should be carried laterally to at least the crural fold, and the inclusion of the mons will thus be apparent on this basis. Excision should be carried into both inguinal areas forming the "horns" on the specimen and the skin overlying the most superficial groin nodes should be removed (Figure 1). How much of the skin should be excised in the inguinal area depends upon the involvement of the inguinal nodes with palpable tumor. Enlarged nodes would suggest more strongly that the skin may be involved with tumor due to lymphatic obstruction and retrograde lymph flow. In these instances larger strips of skin should be removed with the specimen in the inguinal areas.

TABLE 1.—*Five-Year Survival of Vulvar Cancer Associated with Various Treatment Regimens*

Reported by	Percent Five-Year Survival with: Radiotherapy Alone	Vulvectomy Alone	Vulvectomy and Radiotherapy	Radical Vulvectomy and Lymphadenectomy
Smith & Pollack, 1947	16.7	47.6	5.6	52.6
Huber, 1953	19.2	39.4	..	36.4
Taussig, 1940	4.8	8.3	..	58.5
Lunin, 1949	20.0	25.0	..	100
Brandstetter, 1961	10.3	17.6	..	58.3
Way, 1960	..	..	..	74.0

TABLE 2.—*Incidence of Positive Inguinal or Pelvic Nodes in Association with Vulvar Cancer*

Reported by	Total Patients	Positive Nodes	Percent
Cherry and Glucksman, 1955	95	42	44.2
Green et al, 1958	238	140	58.8
Way, 1960	143	60	42.0
Macafee, 1962	82	33	40.2
Rutledge, 1970	127	45	36.0

The accepted indications for inguinal and pelvic lymphadenectomy as a standard part of the surgical treatment have undergone considerable changes. Most investigators agree that the radical vulvectomy should be accompanied by bilateral inguinal lymphadenectomy. An exception is the feeling expressed by Morris[6] and others that unilateral inguinal lymphadenectomy may be indicated for small lesions localized to one side of the vulva. The rationale for this therapeutic approach comes from the fact that the contralateral inguinal nodes are almost never positive when the ipsilateral inguinal nodes are negative. Morris urged analysis of the ipsilateral inguinal nodes before the bilateral dissection, and then withholding contralateral inguinal lymphadenectomy when the ipsilateral inguinal nodes are negative for tumor. It must be added, however, that this opinion is not widely held.

Whether the pelvic nodes should or should not be removed has been discussed extensively in the literature of the past several decades. Lymphatic channels of the labia do not normally drain directly to the pelvic nodes, but do so via the groin nodes. However, other portions of the vulva, such as the clitoris and urethral meatus, drain in part directly to the pelvic nodes. The incidence of positive lymph nodes in the surgical series reported varies from approximately 30 to 60 percent (Table 2) where both inguinal and pelvic lymphadenectomy were performed. Correlation of the incidence of groin and pelvic node metastasis with tumor size

TABLE 3.—*Incidence of Pelvic Node Involvement Associated with Vulvar Cancer*

Series	Patients	Percent with Positive Nodes	Percent with Positive Pelvic Nodes
Taussig, 1940	65	46.2	7.7
Way, 1954	65	32.3	13.8
Way, 1960	143	42.0	16.1
Stening & Elliott, 1959	50	40.0	12.0
Collins, 1963	71	31.0	8.5

shows a general tendency for larger tumors to have a greater frequency of node involvement in both areas. Collins et al[7] found positive nodes in 20 percent of cases of vulvar lesions smaller than 3 cm and in 71 percent when the tumors were larger. The frequency of positive nodes also correlates well with the presence or absence of palpable nodes in the inguinal area. Positive nodes are thus more commonly found in patients with palpable enlargement of inguinal lymph nodes. Of course, when these groin nodes are histologically positive there is a greater likelihood that the pelvic nodes will be similarly positive (Table 3). Conversely, positive pelvic nodes are found only 1 percent of the time when the inguinal nodes are negative.[3] We have thus adopted the policy of performing the pelvic lymphadenectomy in the following circumstances:

- If the inguinal lymph nodes are positive.
- If the clitoris is involved with the lesion.
- If mucous membrane of the urethra, vagina or anus is involved.
- If the primary lesion is larger than 3 cm.

In contrast with its place in other forms of gynecological cancer, radiotherapy is at a disadvantage in vulvar cancer because this relatively radio-resistant neoplasm occurs in a very radiosensitive area.[8,9] While squamous cell carcinoma of the cervix and vagina are just as radio-resistant as squamous vulvar carcinoma, the normal tissues of the cervix and the vagina can tolerate a large amount of irradiation, while the vulva cannot. In dealing with vulvar malignant disease, the therapeutic index is most unfavorable. Some radiobiologists have explained this by stating that this area has a disproportionally large number of end arteries to be exposed to radiation in high doses. Certainly radiation produces a diffuse vasculitis and such a concept is possible. This disease usually occurs in elderly persons in whom the processes atherosclerosis and arteriosclerosis have so compromised the blood supply that radiation injury may be more likely. This and the absence of ade-

TABLE 4.—*Staging (Clinical)* of Vulvar Cancer*

	Primary Tumor	*Regional Nodes*	*Distant Metastasis*	
Stage I	T1	N0	M0	All lesions confined to the vulva with a maximum diameter of 2 cm or less and no suspicious groin nodes.
	T1	N1	M0	
Stage II	T2	N0	M0	All lesions confined to the vulva with a diameter greater than 2 cm and no suspicious groin nodes.
	T2	N1	M0	
Stage III	T3	N0	M0	Lesions extending beyond the vulva but without grossly positive groin nodes.
	T3	N1	M0	
	T3	N2	M0	Lesions of any size confined to the vulva and having suspicious or grossly positive groin nodes.
	T1	N3	M0	
	T2	N3	M0	
	T1	N2	M0	
	T2	N2	M0	
Stage IV	T3	N3	M0	Lesions extending beyond the vulva with grossly positive nodes.
	T4	N3	M0	
	T4	N0	M0	Lesions involving mucosa of rectum, bladder, urethra, or involving bone.
	T4	N1	M0	
	T4	N2	M0	
	M1A	..	..	All cases with distant or palpable deep pelvic metastasis.
	M1B	..	..	

*FIGO 1967

quate collateral circulation make this region particularly vulnerable. In addition, the folds of skin which comprise the vulva afford a particularly unfavorable field for external irradiation, and moist dermatitis invariably occurs. Thus the peculiar characteristics of the vulvar skin are such that cancericidal dosages of ionizing radiation cannot be administered without physically producing undesirable side effects. These undesirable side effects take the form of acute vulvitis, severe pain, and often radiation necrosis with infection and sloughing.

The rationale for a combination of local operation followed by irradiation of the regional nodes has some merit. However, the results do not show that combined treatment is really any better than simple vulvectomy alone. Granted that these procedures are usually performed on patients with advanced disease or serious medical complications, the five-year survival rates are only 30 percent for both partial treatment plans.

Recurrence

Recurrences appear to be of two types, local and distant. The distant recurrences predominantly appear in the first year or two following treatment. They usually take the form of disease in the lymph nodes, beginning with the high pelvic and paraaortic chain. In addition, pulmonary metastasis is not uncommon. The local recurrences tend to begin after three years. The frequency of local recurrences may be minimized by examination of the vaginal and other margins by frozen section at the time of operation. Certainly the area of vaginal mucosa closest to the primary lesion should be examined by frozen section at the time of operation to make sure there is a tumor-free margin. The treatment of recurrences is a frustrating problem. Wide excision has been the mainstay of treatment for local recurrences. Radiation therapy may be of value for palliation of distant metastatic lesions.

Survival Rates

The survival rates in this disease depend upon the analysis of the results in absolute survival as against modified life table methods. It may be stated that the absolute five-year survival rate for all patients treated by radical vulvectomy with lymphadenectomy ranges between 60 and 70 percent. Because of the age group commonly affected by vulvar cancer, intercurrent disease often plays a large role in the five-year survival rate. In the series from M.D. Anderson Hospital, the five-year survival rate for 139 patients treated for cure, when modified by the life table methods, was 83 percent.[18] In the experience at Anderson Hospital, survival was stage-related when using the FIGO system (Table 4). Fifty-three patients with negative inguinal and pelvic nodes were followed for five years or more, and none had recurrence. Thirty patients had positive inguinal nodes and 39 percent survived five years free of disease. Throughout the literature survival for patients with

TABLE 5.—*Survival Rates for Patients with Positive Pelvic Nodes*

Series	*Patients*	*Percent 5-Year Survivors*
Green, 1958	16	12.5
Way, 1957	9	22.2
Way, 1960	8	37.5
Merrill & Ross, 1961	3	33.3
Collins, 1963	6	16.7
	42	21.4

positive pelvic nodes has been reported to range from 12 to 38 percent at five years (Table 5), clearly supporting the concept that pelvic lymphadenectomy can be therapeutic.

Melanoma of the Vulva

Melanoma of the vulva, although a rare malignant lesion, is the second most common cancer occurring on the vulva. The lesion occurs predominantly in the perimenopausal and postmenopausal age group; the average age at diagnosis is 57 years. The growth may arise from a pre-existing junctional nevus, from the junctional component of a compound nevus, or *de novo*. The patient usually becomes aware of it because of pruritis, enlargement of a mole, bleeding, or discovery of the tumor itself.

Melanomas are elevated, pigmented, frequently ulcerated and usually surrounded by an inflammatory margin. The differential diagnosis includes benign nevus, furuncle, pigmented basal cell carcinoma, epidermoid inclusion cyst and a host of other lesions. The amelanotic variety may simulate epidermoid carcinoma. More than 80 percent of vulvar melanomas arise from the labia minora and clitoris. Prognosis is related to the size of the lesion, depth of dermal invasion, extension to the urethra or vagina, the presence or absence of regional lymph node metastasis and distant metastasis. Treatment consists of *en bloc* groin lymphadenectomy and radical vulvectomy. The pelvic nodes should also be dissected. If the lesion involves the urethra or vagina, exenteration may be necessary. The five-year survival rate for lesions confined to the vulva is 75 percent.[22]

Sarcoma of the Vulva

Primary sarcoma of the vulva is an unusual lesion. There have been roughly 150 cases reported in the world literature. An exact listing is made difficult by the confusion in the early reports between sarcoma and other morphologically similar lesions such as melanoma. Lundwall,[9] in his study of vulvar malignant lesions, reviewed his own series and those of other investigators. He found 12 cases of definite sarcoma among 1,120 patients with vulvar cancer, an incidence of 1.1 percent.

Location of these lesions seems to follow the same pattern as squamous cell carcinoma of the vulva. In a series of 12 patients reported by DiSaia,[21] the lesions were found on the labium majus in six cases, on the labium minus in three and on the perineum and clitoral areas in three. There is consensus that the age of the patients ranges from 30 to 50 years with a median between 35 and 38 years. The presenting symptom in most cases is local discomfort. Lesions of the labia minora often result in pain during coitus, while those of the labia majora are more often associated with irritation from undergarments. Pain with defecation was the complaint in patients who had lesions of the perianal area. In general the patient has had symptoms for three to 12 months before she consults a physician about them.

The pathological diagnosis appears to have considerable bearing on the prognosis for the patient. Rhabdomyosarcoma is a rapidly growing lesion that spreads early, and the patient's fate is decided shortly after diagnosis. Leiomyosarcoma, on the other hand, is slow-growing and indolent, with late local and distant recurrences.

Sarcomas are notorious for local recurrence and hematogenous metastasis. However, lymphatic metastasis also may occur. In the series reported by DiSaia,[21] seven patients with vulvar sarcoma were treated by radical vulvectomy and bilateral lymphadenectomy. The one patient with nodal disease survived five years. None of the seven had local recurrence. Radical vulvectomy and bilateral groin lymphadenectomy would be rational therapy for this disease.

Adenocarcinoma

Adenocarcinoma of the vulva is one of the rarest of gynecologic malignant lesions. When it does occur, it usually arises from Bartholin's gland. Data about this neoplasm are necessarily scant and most reported series include squamous lesions considered to be of Bartholin duct origin along with the adenocarcinomas obscuring information relating to the specific histologic types. Women with Bartholin's adenocarcinoma average nearly a decade younger than women with epidermoid cancer of the vulva but the symptoms are quite similar. A history of Bartholin gland inflam-

matory disease during the reproductive years may be obtained, and all too often the cancers themselves are mistaken for abscesses, with the error leading to efforts at surgical drainage and delay in diagnosis. It is imperative to recognize that uncomplicated inflammatory disease of Bartholin's gland is uncommon after the fourth decade and does not occur in the postmenopausal years. Biopsy specimens must be taken from all such lesions in these age groups to exclude neoplastic disease.

Bartholin gland adenocarcinoma tends to come to light at a more advanced stage than epidermoid vulvar cancer. This is probably owing to its location deep to the skin in proximity to the vagina, perineal body, anal canal and pubic ramus. The region is quite vascular and its lymphatic chain may drain directly to the pelvic wall as well as the groin. Because of these considerations the minimal treatment for adenocarcinoma of Bartholin's gland should be radical vulvectomy and bilateral ilio-inguinal (groin and pelvic) lymphadenectomy. Extending the operation to remove portions of vagina, levator, ischial-rectal fat, and even more radical modifications may be required, depending upon the growth pattern of the individual tumor.

Survival data from the literature are of little value because of the small numbers of cases. By collating data from three series[5,23,24] reports of 21 cases that could be evaluated were obtained. Of 15 patients with lesions in Stages III and IV, four were living, but only one longer than five years. Six patients with Stages I and II lesions were living, two of them beyond the five-year mark. None of the patients with clinically suspicious nodes survived five years, although one was still well four years after treatment.

In the category of adenocarcinoma of Bartholin's gland there is a special group that encompasses the so-called adenoid cystic carcinoma. This lesion histologically is similar to the corresponding tumor of the major salivary glands. It tends to remain localized, seldom giving rise to widespread metastasis. Lymphatic spread does occur and lymphadenectomy should be included in the surgical treatment.

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Seminars in Virology

The Mystique of the Herpesviruses

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Probing the biologic mystique of the herpesvirus family, we find elements of antigenic similarity, the capacity of virions to persist within our cells in complete form, and the potential at some later time for these virions to undergo renewed replication. A venereal mode of transmission from one host to another may be characteristic of some of these viruses. Similar patterns of illness may be produced by several of the herpesviruses. Within the cellular framework of inflammation and necrosis which infective virus may evoke in the host, there may also reside the capability of neoplastic transformation.

THE HERPESVIRUS FAMILY has evolved from what seemed to be very divergent origins ten to twenty years ago. All members of this group of viruses share some antigenic relationship, and to the electron microscopist they present similar morphologic characteristics of size and shape. Most crucial for the human host, they share biologic characteristics. Primary infections are often silent and the more unique expressions of illness with these viruses may unfold upon reinfection or reactivated infection. Virus may persist in incomplete resting or subviral form. Some of the members of this diffuse family of viruses retain a venereal mode of transmission and some indeed may be oncogenic. We wish to illustrate the convergent relationships which exist within the herpesvirus group by reviewing each member virus and the biologic problems which these viruses pose for man.

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Herpes Simplex Virus, Type 1 and Type 2

The relationship of herpes simplex virus (HSV) type 2 to cancer of the cervix is intriguing and implicates not only the oncogenic potential of this virus but also its apparent mode of venereal transmission. The provocative epidemiologic studies of Rawls and his colleagues[1] have pointed out the striking difference in immunologic experience with HSV type 2 between a control population and a group of women with cervical carcinoma. The uniqueness of this serologic observation is ampli-

fied by the fact that members of both groups had had equivalent previous immunologic experience with the oropharyngeal serotype of HSV type 1. Naib and coworkers[2] observed that 7 percent of women with obvious genital HSV type 2 infection had *in situ* carcinoma of the cervix. Only 0.6 percent of women who had not had genital herpesvirus infection had a similar precancerous lesion. In further confirmation of the venereal mode of transmission, Nahmias et al[3] demonstrated that 3 percent of nuns had antibody to HSV type 2 whereas Rawls and coworkers[4] demonstrated that 43 percent of prostitutes had type 2 antibody. While the population begins to acquire antibody to type 1 virus at an early age, antibody to the type 2 virus appears at the time of pubescence and escalates strikingly during the sexually active years which follow.

Very recently Rapp and his colleagues[5] demonstrated that HSV type 2 is capable of transforming hamster embryo fibroblasts into neoplastic cells.

The biologic characteristics of HSV type 2 differ from those of type 1 strains. They are ordinarily genital strains, produce much larger pock lesions on the chorio-allantoic membrane of the embryonated chick, are more paralytogenic for adult rabbits, and are more likely to disseminate in a direct, non-viremic fashion to the central nervous system. Thus this serotype may be more neurovirulent than type 1 strains.

These biologic characteristics are of great importance to the physician who must deal with perinatal HSV infections. Nahmias, Alford, and Korones[6] reported that the great majority of isolates from neonatal infections are type 2. The illness afflicts mainly pre-term infants; the ratio of infected pre-term to term infants is 1:1.5. This observation is supported by our own studies, which indicate a more striking innate susceptibility of immature tissues to HSV replication.[7] The incidence of perinatal HSV infection is estimated to be 1 in 7,500 deliveries. Hence it might be anticipated that 120 cases will occur in the United States each year. We suspect that with heightened promiscuity and the element of venereal transmission the incidence of neonatal infections is far greater.

We understand the natural history of neonatal HSV infections in only a very superficial manner. When pathologic descriptions serve as the primary source of cognitive clinical information, one must assume that non-lethal cases have eluded the detection of clinicians. Although Nahmias and colleagues[6] suggested that infants with disseminated HSV infection almost uniformly die, one must wonder how often the clinician and the virologist fail to detect mild to moderate disseminated infection, with or without neurological involvement. If such children do not have oropharyngeal or cutaneous lesions, there is no way at present whereby one may make a diagnosis, and indeed many of these cases may survive without the availability of the precise biologic diagnosis ordinarily attained at the necropsy table. Nature suggests that we are dealing with only the tip of the iceberg when we consider that newborn infants with localized infection of the central nervous system, eye, skin, or oral cavity do not uniformly die and may recover health. As experience with the use of pyrimidine analogs for systemic antiviral chemotherapy continues to evolve, there must develop a solid perspective for the natural history of this illness if valid conclusions are to be drawn about chemotherapeutic efficacy. There is the obvious need for a nationwide collaborative study wherein the many medical centers which deal with these infants may coordinate methods of study and pool careful clinical and virologic observations.

The incidence of cervical-vaginal shedding of HSV type 2 is slightly less than 1 percent. This rate of shedding is to be contrasted with the 2 to 5 percent of our population which shed HSV type 1 in the oropharynx. We must determine whether a pregnant woman is more likely than the non-gravid to shed virus in her cervical-vaginal tissues. It will also be important to determine how the quantity of virus in the birth canal relates to subsequent mild or serious infection of the newborn.

Some very important points have been brought to light during recent years which have clarified our understanding about the traffic patterns of virus dissemination from the respiratory tract or the genital tract to neural tissue and in the opposite direction. It is known that fully mature virions may be distributed down the course of peripheral nerves either by streaming through the axoplasm or by cell to cell transmission within the Schwann sheath cells which surround the nerves. This fundamental phenomenon explains, of course, the occasional zosteriform morphologic feature of cutaneous HSV infection. Recently, Stevens and Cook,[8] with some elegant experiments, pointed out that HSV, probably in the form of non-encapsidated and non-enveloped genomic subvirion, may become latent in ganglion cells. Utilizing the innovative technique of ganglion tissue culture, these workers were able to unmask latent HSV particles within the ganglion

tissue of experimental animals. Traditional virologic techniques failed to detect mature, complete virus.

Varicella-Zoster

Infections produced in man by varicella-zoster, a member of the herpesvirus family, represent the classic example of the biologic point developed above—namely, that primary infection, chickenpox, is followed by latency in neural tissue for many years only to re-express itself with the sharply different and very classic dermatomorphology of herpes zoster (shingles).

Cytomegalovirus

In the context of the exploration of the natural history of HSV infections in the neonate, it is illuminating to review our understanding of congenital cytomegalovirus (CMV) infection in 1972 and compare that with our understanding of this disease ten years before. It was 1962 when Weller and Hanshaw[9] described, in what is now considered one of the classics in the CMV literature, the full sweep of this infection in newborn infants. Clinicians considered this to be a rare illness characterized by severely damaged and stunted infants with hepatosplenomegaly, microcephaly, intracranial calcifications, thrombocytopenic purpura, hemolytic anemia, and severe neurologic impairment. At present we know that congenital CMV infection is indeed very common, occuring in perhaps 1 percent of all newborn infants.[10] Few of these infants present the expanded syndrome of devastating disease as was originally described. Rather, a majority are perfectly normal. A few may have only intrauterine retardation of growth. Emanuel and Kenny[11] described infants with only idiopathic hyperbilirubinemia. Although other investigators have not fully supported his observations, Hanshaw[12] has suggested that some infants and children affilicted as fetuses with CMV infection develop only otherwise unexplained microcephaly. Although congenital CMV infection does not seem to be as awesome a clinical problem as it was reported to be a decade ago, careful evaluation of these otherwise normal infants reveals that approximately 20 percent have incurred some neurologic damage and mental retardation.[13] Other isolated sequelae of congenital CMV infection include neonatal hepatitis and a surprising incidence of inguinal hernia.[14] Much as has been described with congenital rubella virus infection, CMV infected infants may be deaf and may also have the metaphyseal radiolucency of long bones which has been considered to be so characteristic of congenital rubella.[15,16] However, cardiovascular defects are not a prominent part of the clinical spectrum of congenital CMV infection.

There must be some reason for this remarkable incidence of infection, and Numazaki and his colleagues[17] have observed that during the course of gestation there is an increasing incidence in the rate of shed of this virus in the vaginal secretions of the pregnant woman. Although they were unable to detect vaginal shedding of CMV during the first trimester of pregnancy, they pointed out that 28 percent of women were shedding this virus by the end of gestation. Medearis and his colleagues,[18] in Pittsburgh, have also found a significant percentage of women shedding CMV in their vaginal secretions during pregnancy. Reynolds et al[19] have detected a similar striking increase in the shedding of virus from the cervix throughout the course of pregnancy. It cannot be concluded absolutely either that these maternal infections with CMV represent acquired illness or that they reflect reactivation of virus replication during the late phases of pregnancy. Careful serologic studies suggest that cervical-vaginal CMV shedding occurs as a reactivation phenomenon in that detectable levels of CMV complement-fixing antibody remain stationary throughout the period of gestation.[17,19]

Another intriguing component to congenital CMV infection is the possibility of venereal transmission. In one study the incidence of congenital infection was found to be 1 in 114 cases of unmarried women, in contrast to the incidence of congenital infection in married women of 1 in 700.[20]

An important new syndrome is that of CMV mononucleosis.[21] This illness is characterized by fever without the presence of pharyngitis and adenopathy which one anticipates in typical infectious mononucleosis. The heterophile antibody test is ordinarily negative but atypical lymphocytes are present. Very closely interlinked with CMV mononucleosis is the post-perfusion syndrome which has also been attributed to infection with CMV. The syndrome is an infectious mononucleosis-like illness with fever, splenomegaly and the presence of atypical lymphocytes, but a negative heterophile antibody test. This syndrome is associated with the transfusion of fresh blood, usually no more than two to three days old.

There are some observers who still believe that this post-perfusion syndrome represents reactiva-

tion of CMV replication within the host rather than the acquisition of virus via the leukocytes of fresh blood.[22] The incidence of the disease seems to relate clearly to the number of units of whole blood used during the surgical procedure. It has been observed that 5 percent of blood donors carry CMV in their leukocytes.[23] Indeed, Lang et al[24] have demonstrated that the elimination of leukocyte precludes the acquisition of infection by recipients. All of these facts would suggest that the post-perfusion syndrome represents an illness acquired as a result of the direct transfusion of virus into the host.

The intriguing experience of the Henles and coworkers[25] gives additional support for the notion that this illness is an acquired infection. They found that 36 percent of cases of post-perfusion syndrome were CMV in origin, so indicated by CMV antibody rise. It is amazing to note that of all the patients which they studied, 40 percent were CMV serosusceptible. Thus, their figures for attack rate correlate very closely with the segment of the patient population originally deemed to be susceptible. Only 8 percent of the post perfusion cases were caused by the Epstein-Barr virus (EBV). They found that 10 percent of the entire study group were susceptible to EBV, and so once again the great majority of susceptible persons incurred infection once exposed to the virus by transfusion.

Epstein-Barr Virus

Pathogenic relationships have been established between the Epstein-Barr virus (EBV) and infectious mononucleosis as well as Burkitt's lymphoma and nasopharyngeal carcinoma. The original observations at Yale University had the greatest impact on the establishment of an etiologic relationship between this virus and infectious mononucleosis.[26] It was observed that antibody-negative freshman students were the only students who acquired this infection at any time during the remainder of their collegiate years. Freshman who were antibody-positive at the outset did not acquire infectious mononucleosis. Therefore, much as in the post-perfusion syndrome, disease seemed to occur only in persons in whom susceptibility was demonstrated by the lack of protective antibody. Dr. James Grace[27] performed an important experiment when he transmitted the disease of infectious mononucleosis by the inoculation of EBV into a youngster with lymphatic leukemia. Recently, Shope et al[28] reproduced the disease in the rhesus monkey by introducing infected leukocytes. Serologic diagnosis, employing the EBV complement-fixing antibody assay, may be unrewarding in the evaluation of infectious mononucleosis. Antibody titers appear so quickly at the outset of symptomatic infection that it is difficult to demonstrate a significant four-fold rise during the early weeks of illness.

One of the great students of this disease has been Dr. Alfred Evans. Without the knowledge of a specific pathogen or the presence of virologic and serologic tools to carefully study such an illness, Evans[29] suggested many years ago that primary illness in the child was much different than that in the adult. Youngsters presented with fever and rash, perhaps splenomegaly and lymphadenopathy, and the appearance of atypical lymphocytes. The heterophile antibody tests were ordinarily negative. As the potential host aged through puberty into the early adult years, Evans documented the classic illness with fever, sore throat, splenomegaly, lymphadenopathy, atypical lymphocytes, and now the elaboration of heterophile antibody.

Now with the necessary virologic and serologic tools available, similar epidemiologic studies have been performed and they accurately confirm the earlier predictions and observations of Evans. Primary EBV infection in a very young child may produce nothing more than an undifferentiated febrile illness. During the early school years a further differentiated form of disease, with lymphadenopathy, splenomegaly and atypical lymphocytes, occurs. As Evans had anticipated, heterophile antibodies are usually negative. Careful seroepidemiological studies of EBV infection by Deinhardt and coworkers[30] demonstrated both in Chicago and in Alaska that the great majority of children and adults have antibody to this virus. This is surprising in light of the original observations of the Yale investigators which indicated that only 25 percent of beginning students at New Haven had antibody to this virus.

Recent observations by Hanshaw and his colleagues[31] provide continuing support for the taxonomic relationship of EBV, CMV and varicella-zoster virus within the entire herpesvirus family. These investigators detected macroblobulin(IgM) CMV antibody rise early in the course of illness with EBV infection. They were unable to detect complement-fixing CMV antibody response, ordinarily a 7s (IgG) antibody, in persons with documented EBV infectious mononucleosis. The same observation was made with varicella-zoster virus

infection. Early in the course of chickenpox and shingles there appeared a rise of IgM CMV antibody without a concommitant rise of CMV complement-fixing antibody. Because IgM antibodies may reflect a more primitive and broad antigenic relationship existing among all of these herpesviruses, one might anticipate an early IgM antibody response to any of the other viruses within the family in the event of a primary illness. Rather than dual infection with two herpesviruses, it seems that infection with one herpesvirus calls forth a primitive, abbreviated immunologic response to other members of this virus family with which the host has had an antigenic experience in the past.

Some patients with adenopathy, splenomegaly, hepatomegaly, occasional rash, sore throat, a few atypical lymphocytes and negative heterophile antibody, but no EBV antibody rise, may reflect a unique response to infection with coxsackievirus B5.[32] Other patients with atypical lymphocytosis and fever alone may have CMV infection and the diagnosis may be elucidated by searching for CMV antibody. When confronted with infectious mononucleosis-like illness and its various manifestations, one should consider EBV, CMV, coxsackievirus B5, and also primary toxoplasmosis.

The post-perfusion syndrome associated with EBV is characterized by fever, splenomegaly, and atypical lymphocytes.[25] As was noted for CMV, 5 percent of blood donors have been shown to be carriers of EBV. EBV persists in lymphocytes and may mature and release from cells when cultured *in vitro,* a phenomenon quite similar to the fundamental cellular relationship of some of the other herpesviruses with neural tissue in the human host.

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MEDICAL PROGRESS

The Neurological Evaluation of Children with Learning Disorders

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FROM A CLINICAL POINT OF VIEW, the term *learning disorder* means that there is good evidence that a child's learning performance at school is not commensurate with his intellectual abilities. Children with such problems are being brought to to physicians in increasing numbers for assistance in the identification of factors contributing to poor classroom performance. Parents and teachers expect the physician to be able to help them unravel the difficult issues of distinguishing between neurological handicaps, behavioral disturbances and faulty educational procedures as causes for school learning problems. These distinctions are often difficult, for all three of these factors are commonly found to have contributed to an educational problem. The physician who accepts the role of neurological consultant should regard a learning disorder as a symptom, the cause of which is his responsibility to elaborate to the fullest possible extent.[1]

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A recent review of various studies of reading disorders in the United States has resulted in an estimate that 15 percent of school age children are affected by learning disorders[2]; other estimates have ranged from 5 to 30 percent. In addition, it is clear that these children are not uniformly distributed throughout the country and that prevalence is largely determined by social and economic factors. No simple formula will serve to explain the nature of this pervasive problem. Many physicians are reluctant to become involved with the problem of learning disorders because of a sense of inadequacy to cope with the issues at hand. Others have become overly committed to some specific mode of treatment in which comprehensive consideration of the child's problem is avoided. The field of learning disorders is one that has been especially susceptible to extravagant claims by therapists of all types.

The physician serving as a neurological consultant has several roles in the evaluation of children with learning disorders. It is his responsibility to detect the presence of neurological conditions that may be present in these children. He is expected to be an expert authority on theories

relating brain dysfunction in children to learning problems. Finally, the neurological consultant is expected to point the way to appropriate treatment programs that will permit a child to achieve his full potential at school as well as at home.

The purpose of this review is to outline the role of the neurological consultant in the evaluation of children with learning disorders. This will be considered under the following headings: The Neurological Examination; Differential Diagnosis; Learning Disorder Syndromes.

The Neurological Examination

The actual neurological examination of the young school-age child is quite similar to the conventional neurological examination for adults. Essentially the same outline of procedures is utilized in spite of frequent implications that there are special methods used by the pediatric neurologist (this is true more for examinations of infants). The unique feature of the pediatric neurologic examination is the special attention given to evaluating developmental milestones and developmental disorders. The diagnosis formulated by the neurologist is often largely based upon obtaining a discriminating history of the child's progress in motor, language and social areas. The occurrence of possible brain-damaging events and pertinent family history will contribute to the final formulation. Occasionally, evidence of overt neurological deficits or of progressive neurological disorders will be recognized.

A few remarks are in order regarding interpretation of the neurological examination in children. Certain signs can be regarded as indicative of neurological disease regardless of age or state. For example, the presence of spasticity, dystonia, muscle wasting or muscle fasciculations can be regarded as abnormal at any age. A fully developed extensor plantar response can be accepted as an abnormal sign after the first two years of life. However, there are many aspects of the neurological examination, particularly in the evaluation of of proprioceptive functions, that are difficult to interpret in the elementary school child. It is particularly important to keep in mind that motivation and mental state will greatly influence the ability of a child to perform complex motor acts. An important guideline for the examiner is to distinguish between loss of previously acquired abilities and the failure of acquisition of abilities. Much of the traditional neurological examination of complex motor functions is based upon demonstration of loss of abilities of well defined deviations from the norm. These criteria are often not fulfilled in the diagnosis of "borderline" neurological abnormalities claimed to be present in children with learning disorders. There are virtually no normative data meeting ordinary standards of reliability regarding acquisition of abilities such as the performance of rapid pronation-supination of the hands, performance of tandem walking, the behavior of outstretched hands, the occurrence of overflow movements, and other "soft" neurological signs. When normative data are available, as in the establishment of laterality functions,[4] there is often evidence of wide variations in the timetable of acquisition.

It is an important responsibility of the neurological consultant to distinguish between hard evidence of neurological abnormality and the hazier "soft" neurological signs. In general, he is best advised not to allow suspicion of these latter signs to justify a diagnosis of brain dysfunction, minimal or otherwise.

The examination of an elementary school child should be approached circumspectly. It is best to engage the child at the outset in a conversation about a familiar subject—asking his age, grade and name of his teacher may be a good beginning. This can lead into questions regarding his favorite television program, names of friends, favorite games and relationships with siblings. Pencil and paper tests and brief reading tests can be administered at this time. After a relationship has been established, the child may be more inclined to disrobe for the neurological examination.

The following is an outline of the historical data that should be obtained and the examinations that should be carried out:

Historical data

Pregnancy history

Perinatal history—Mode of delivery, complications, birth weight, estimate of maturity, condition at birth, neonatal problems.

Developmental milestones—Data on motor and language development. Age at walking unsupported seems to be the most reliable milestone elicited retrospectively.[5]

Developmental disorders—Indications of speech disturbances, and data on delayed speech, poor speech comprehensions, hearing difficulties, delay in establishment of hand preference beyond two to three years of age, early over-activity, enuresis, pica, sleepwalking, temper tantrums, breathhold-

ing spells, physical awkwardness in motor tasks or games.

Medical history—Head injuries associated with loss of consciousness, meningitis or encephalitis, recurrent ear infections, visual disorders, medication history, intoxications.

Family history—Educational history of parents and siblings, of family psychiatric disturbances, and of neurological disorders in family.

School history—Performance in earlier grades and nursery school. When did learning problem in school begin?

Present status—School grade placement, behavior at home and at school, peer and family relationships, physical complaints (headaches, abdominal pains, ocular problems). Present medications. Other evaluations.

General Examination

Height, weight and head circumference—These should be plotted on growth curves.

General inspection—Unusual cranial configurations. Inspection of skin for cutaneous abnormalities such as *cafe-au-lait* spots, or vascular nevi. Appearance of the genitalia. General nutritional status.

Mental status—Affect, ability to relate, and fund of information for age. Note activity level, distractibility, evidence of autistic behavior or other signs of a thought disorder.

Speech—Evidence of dysarthric, dysrhythmic or aphasic speech patterns.

Cranial nerves—Visual acuity, evidence of strabismus, smoothness of visual pursuit, presence of facial asymmetries. (These items of especial importance.) Note presence of nystagmus or poor tongue control.

Motor functions—Evaluate muscle strength and tone in all four extremities. Overt paresis will usually be associated with reduced muscle mass and abnormalities of muscle tone. An extremity that has been dysfunctional since infancy due to central nervous system abnormalities will be shorter than its opposite mate. If asymmetries are suspected the circumference and length of extremities should be measured with a tape measure.

Lesser diminution of muscle strength may not be associated with obvious disturbances of tone or strength but may be the cause of coordination difficulties. It is important to distinguish coordination problems due to weakness from those due to ataxia. A clue as to the nature of the problem may come from the assessment of muscle tone and reflexes. Ataxia is often associated with hypotonia whereas weakness of cerebral origin is associated with hyperreflexia and often, although not invariably, abnormal increase of muscle tone. Children with ataxia do not manifest any evidence of diminished strength when muscle strength is evaluated independently of coordinative abilities.

The assessment of muscle tone is one of the most important aspects of the neurological examination of children. The responses of large muscle groups to both fast and slow stretching is evaluated. Spasticity refers to the presence of a hyperactive stretch reflex; stretching of the muscle sets into action a reflex shortening of the muscle fibers. This reflex resistance to stretching is evident at the beginning of the stretch but then disappears, resulting in the "clasp-knife" type of increased muscle tone. It is particularly evident in the antigravity muscles—for example, the extensors of the leg and flexors of the arm. Rigidity refers to a constant increased resistance to muscle stretching, sometimes in the form of intermittent resistance known as "cogwheeling." Rigidity is traditionally associated with extrapyramidal disease states that may also produce movement disorders.

Hand preference can be determined by questioning a parent and noting hand used in writing and throwing. Foot preference can be evaluated by asking a child to kick a ball. This information is of little significance, however, aside from its use in detecting a hemiparetic condition.

Gait should be observed, with attention to evidence of abnormal gaits suggestive of cerebral palsy syndromes. Also to be noted is the ability to run and rapidly reverse direction, and ability to walk on toes and heels. It should be remembered that a child's gait is especially sensitive to a feeling of self-consciousness when under observation.

Coordinative skills can be assessed by ability to handle buttons and shoelaces or catch a ball. The presence of ataxia or incoordination of voluntary movements is additionally evaluated by performance of finger to nose movements with the hands outstretched, performance of tandem walking, hopping on either foot and rapid supination-pronation movements of hands on knees.

Involuntary movements — Involuntary movements can be noted by observing a child in a stationary state with hands resting lightly on knees or outstretched in front. Sometimes involuntary movements are better noted while engaging a child in conversation that is mildly stressful. Some chil-

dren will attempt to inhibit these movements by holding one hand with another or shifting in the chair. The examiner should release the hands and place them separately on the child's knees when involuntary movements are being sought. Choreic movements are rapid, brief, irregular muscular jerks of the face or extremities. Athetoid movements refer to slower, twisting movements often imposed upon voluntary movements, causing unnatural posturing. Tics are stereotyped muscle twitching involving the same muscle groups repetitively, often affecting facial or ocular muscles.

Overflow or associated movements are a type of involuntary movement occurring in one area of the body when a voluntary movement is initiated in another area—for example, finger tapping or touching of thumb to forefinger. Mirror movements are a type of overflow phenomenon in which the associated movement occurs on the opposite side. These movements have been regarded as abnormal after the age of nine years[6,7] but much depends upon the particular movement elicited. In general, published studies indicate a wide age range of acquisition of ability to inhibit overflow phenomena. Connolly and Stratton[8] utilized a number of specified movements for observation such as the movement of a contralateral thumb when pinching a clip, movement of arms upon walking on inverted feet, and several finger moving exercises. They reported a gradual disappearance of associated movements in ordinary school children up into the midteens. Each movement had its own timetable of disappearance. Inhibition of overflow is also a function of mental age; hence, mentally retarded children can be expected to manifest these movements more freely than children of normal intelligence.

Normally, mirror movements may be seen more readily in the dominant hand or leg. However, an unusually strong asymmetry of associated movements should alert the clinician to the possibility of hemiparesis on the side not displaying the mirror movements.

Reflexes—The presence of decidedly asymmetrical deep tendon reflexes is more significant than symmetrical variation of reflex activity. It may indicate the presence of hemiparesis. The presence of clonus upon eliciting lower extremity deep tendon reflexes or upon firmly dorsiflexing the foot should be noted. Ankle or knee clonus is always abnormal in school age children.

Twitchell et al[9] described a posturing of the outstretched hands in which the hands assume a position of overpronation with flexion of wrists and extension of fingers. This is termed the "avoiding response" and has been regarded as persistence of an infantile reflex, indicating the presence of "minimal cerebral dysfunction."

Tests of Body Awareness and Right-Left Orientation

Two-point discriminations. The ability to distinguish between double simultaneous somasthetic stimulation is a standard procedure in attempting to detect parietal lobe dysfunction in adults. The closer together the points of stimulation, the more sensitive the test. Discrimination of simultaneous stimulation of two fingers of one hand is said to be possible for over 95 percent of children more than seven years of age.[10] Similar discrimination between face and hand stimulation is said to be possible for normal children over six years of age.[11]

Tests of sensory discrimination utilizing double simultaneous stimulation have not been extensively employed due to the difficulty of establishing reliability of the procedure (the work of Kinsbourne and Warrington is an exception). Nevertheless, tests of this sort offer considerable theoretical advantages in the investigation of global perceptual abilities because motor performance is not an integral part of the test procedure.

Right-left discriminations—The ability to indicate the right and left parts of the child's body is usually present by seven years of age[4,12,13] although the range in normal children extends up to ten years. The ability to perform double crossed tasks (for example, "Touch your left ear with your right hand") and to recognize the examiner's body parts ("Touch my right knee with your left hand") develops later and in a more variable manner.[14]

Perceptual Functions — Considerable insight into perceptual abilities can be obtained by pencil and paper drawing tests. A five-year-old child should be able to copy a square, a six-year-old a triangle, seven- to eight-year-old a diamond. Older children can copy an octagon. Ability to trace a simple figure under a sheet of paper or trace a line between converging lines as described by Paine[15] assesses similar skills. Interpretation of pencil and paper copying tests requires experience and should usually be supplemented by formal psychometric testing. The ability to write from dictation develops between six and eight years of age. Use of this method to detect perceptual diffi-

culties is ordinarily useful only after this age group. Examination of handwriting patterns has been extensively used as a means for identifying children with dyslexia. It is a technique that is heavily dependent upon the experience and judgment of the examiner.

Differential Diagnosis

The detection of conditions that may produce or be associated with learning disorders in children is one of the prime responsibilities of the neurological consultant. Diagnostic approaches become clear when the physician has a clear notion of the differential diagnosis to be considered. The important syndromes to be considered are as follows:

Mental retardation
Cerebral palsy
Seizure disorders
Auditory disorders
Ocular disorders
Progressive neurological disorders

Mental Retardation

It is of the greatest importance to distinguish children whose learning difficulties are due to intrinsic limitations of intelligence from those who manifest specific learning problems. Many parents of children with mild but global retardation syndromes prefer to regard their children as possessing specific learning disabilities. Some retarded children are trained in verbal skills far beyond their actual abilities in judgment and performance.

A careful developmental history will often reveal evidence of delayed motor and speech development. Any child who was not walking unaided by 18 months of age is highly suspect of some major deficit in mental or neurological functions. Persistent inability to develop peer relationships is suggestive although by no means pathognomonic of mental retardation. Conversation with a child will often suggest to the physician the presence of dulness of mental faculties.

Whenever the presence of a mental retardation syndrome is suspected, use of one of the standard psychometric tests of intelligence is required. This is often the Wechsler Intelligence Scale for Children (WISC) which has the special virtue of being divided into verbal and performance sections. The Stanford-Binet is often utilized for younger children—6 years or under. These tests are not infallible indices of mental retardation, as performance on them may be affected by other factors; but no diagnosis of mental retardation should be considered without measuring the intelligence quotient. IQ's of 65 to 82 are generally considered in the educable range of mental retardation.

The physical examination of children with suspected mental retardation should include careful inspection of the skin for evidence of neurocutaneous syndromes. The presence of multiple *cafe-au-lait* spots, subcutaneous nodules or heavy freckling may suggest neurofibromatosis. Short stature and thickening of the neck folds in a girl should raise the issue of Turner's syndrome (45 chromosomes, XO karyotype). Buccal smear examination revealing a chromatin-negative pattern in a female will establish this diagnosis. Turner's syndrome is of special interest in learning disorders because of the recognition of a specific impairment of spatial abilities and of right-left directional sense in affected children.[16] It is this "space-form" deficit that may account for the high incidence of mild mental retardation in children with Turner's syndrome.

Other specific medical disorders to be considered in mild mental retardation are hypothyroidism, hypoparathyroidism, phenylketonuria and disorders affecting sex chromosomes. These conditions can be identified by appropriate laboratory procedures.

Cerebral Palsy

The term *cerebral palsy* refers to a group of disorders of motor function due to non-progressive brain lesions acquired in early life. It is common for children with overt cerebral palsy syndromes to manifest evidence of learning disorders. There are several reasons for this association. Many children with cerebral palsy have borderline intelligence levels. A motor handicap is a serious problem for a child attempting to adjust to the classroom routine. Hyperkinetic disorders present in these children may interfere with school adjustment. In addition to these obvious reasons for school failure, there is evidence of specific perceptual deficits in children with cerebral palsy.[17]

While overt forms of cerebral palsy are readily recognized, borderline forms present greater difficulties in diagnosis. It is important to remember that the manifestations of cerebral palsy may lessen or even disappear during later development. Thus it is not surprising that borderline manifestations of these syndromes may exist. It is important that these be recognized by the physician even if the relationship to the learning disorder is not clearly established at the time of examination. These may be categorized as "soft" neurological

signs by those not familiar with the various manifestations of mild CP syndromes.

Clumsiness. This expression generally refers to awkwardness of physical performance in activities involving gross muscle units—running, ball-playing, self-dressing, and the like. Walton and coworkers[18] described the "clumsy child syndrome" in children with learning difficulties who also manifested evidence of constructional apraxia, dysgraphia and dyscopia. Clumsiness is particularly prominent in ataxic forms of cerebral palsy. It is important to recognize the presence of ataxia in clumsy children. This symptom is due to a disturbance of postural fixation which, in children, is usually due to cerebellar fixation. This can be easily demonstrated by standard neurological tests of cerebellar function such as the finger-to-nose maneuver, pronation-supination of the forearm, touching each finger against the thumb in sequence, and ability to maintain hands in an outstretched position. Tandem walking (heel-to-toe) and ability to hop on one foot are especially sensitive tests of cerebellar functions.

Clumsiness is a highly nonspecific symptom that may be found in most mentally retarded children, may be associated with anxiety or may be present in children who are normal in all other respects. It is not appropriate to consider this symptom as indicative of some type of cerebral dysfunction unless definite supporting evidence of brain dysfunction is present such as hyperactive stretch reflexes, extensor plantar responses or definite ataxia.

Involuntary movements. Some children with learning problems are restless and fidgety much of the time. They may manifest choreic-like adventitious movements that may be elicited by asking the child to extend his arms or place them on his knees for a moment or two. Environmentally induced stress will often bring out these movements. Sometimes voluntary activity results in "overflow" phenomena—that is, the occurrence of unwanted movements in addition to the desired movements. Mirror movements refer to overflow into the opposite side of the body and may be particularly prominent in hemiparesis with overflow into the normal side. Involuntary movement disorders due to brain lesions must be distinguished from tics of psychogenic origin. The latter are stereotyped muscle twitches usually involving the same muscle groups that are characteristically seen in the facial and ocular muscles.

Gait disturbances. Observations of gait and posture will uncover mild forms of cerebral palsy when gross abnormalities are not evident. Walking is a complex neuromotor task involving many reflex and integrative functions. Toe walking, hemiplegic gaits (circumduction of leg and diminished swinging of arm), wide-based gaits and difficulty with tandem walking may be manifestations of cerebral palsy syndromes. Observation should be made of walking, running, ability to rapidly reverse direction, and tandem walking. The condition of the soles of the shoes should be inspected for evidence of asymmetric wear. The different gait abnormalities found in cerebral palsy syndromes are described in detail by Paine and Oppe.[9]

Seizure Disorders

As in cerebral palsy, there are several reasons why children with seizures may do poor work in school. The occurrence of frequent seizures tends to interfere with mental processes. Hyperkinetic behavior is common in children with recurrent seizures. The administration of high doses of anticonvulsant agents may in itself interfere with cognitive functions. The existence of learning problems is likely to be ignored in epileptic children whose seizures are difficult to control, even though the school problems may be more disruptive to the child than the seizures.

An important responsibility of the physician examining children with learning disorders is the detection of unrecognized seizure phenomena. The hallmark of seizure phenomena is abrupt alteration of behavior. Temporal lobe seizures may manifest themselves as behavioral automatisms such as lip-smacking, chewing movements or abrupt disorientations. The child may appear confused, drowsy or upset afterward. There are some reports of prolonged behavior disturbances representing seizures,[20] but this is a rare event.

When a seizure disorder is suspected, obtaining an electroencephalogram will commonly although not invariably reveal evidence of epileptiform discharges. This means that paroxysmal hypersynchronous discharges, generalized or focal, are seen in the tracing. Mild dysrhythmic disturbances in the electroencephalograms of children have little clinical significance at present.

The occurrence of major EEG abnormalities such as polyspike or spike and wave discharges can be found in 5 to 10 percent of children with learning disorders in the absence of overt clinical manifestations of seizures.[21,22] Paine[23] suggested that this phenomenon represents a borderline form of epilepsy. The effect of subclinical EEG seizure

bursts upon the learning process is not understood at present but it would be surprising if some relationship did not exist.

Auditory Disorders

Hearing deficits may produce classroom impairment in the absence of gross deafness. These are usually due to high-frequency hearing loss as indicated by a sloping configuration of the audiogram.[24] High-frequency deficits result in loss of consonant recognition that is functionally more disabling than low-frequency losses. Severe high-frequency losses are always associated with some degree of speech impairment. Less severe deficits may not noticeably affect speech but may require intensive concentration by the child in order to hear. Such children may seem to lose interest in classroom activities or be accused of uncooperative behavior when in fact they cannot maintain the effort required to hear the teacher.

Screening audiometry should be performed on all children with unexplained learning problems. This is a simple office procedure that can be carried out by a nurse or assistant. Any evidence of a deficit indicates the need for full-scale audiologic evaluation. Failure to recognize hearing deficits in children with school problems will result in expenditure of much misdirected effort with little to show for it. It is surprising how long high-frequency hearing deficits in children may go undetected.

Ocular Disorders

There is a consensus among ophthalmologists who have looked into the relationship of ocular disorders to reading problems that minor disturbances of visual acuity or ocular muscle imbalance do not themselves produce reading problems although they may aggravate an existing situation.[25] Many claims have been made relating poor ocular skills, eye-hand coordination problems or constricted visual fields to learning problems, but there is little evidence that ocular training programs in themselves are of value in assisting children to learn. Intermittent squints and refractive errors are equally common in children with and without reading problems.[26]

The above statements do not mean that evidence of squint, eye-strain or poor visual acuity does not call for appropriate treatment. It should not be expected, however, that these measures will prevent or reverse reading disorders in children except in very rare cases.

Progressive Neurological Disorders

Progressive neurological disorders are rare but their detection should not be missed by the consulting physician. There are a number of degenerative neurological disorders whose onset may be heralded by learning problems during childhood. The gradual worsening of symptoms, such as emotional lability, movement disorders or coordination problems in a child without obvious environmental difficulties suggests a central nervous system degenerative disorder. These include Huntington's chorea, Wilson's disease, subacute sclerosing panencephalitis and juvenile cerebromacular degeneration.[1] Family and genetic counseling are of great importance in these disorders.

Brain tumors in the cerebral hemispheres may produce subtle signs of personality disturbances for years before the true nature of the problem is recognized (often by onset of a seizure). Intractable headache is a common associated complaint. The behavior of children with brain tumors is often characterized by apathy and a tendency to withdrawal. Electroencephalograms, skull radiographs and radioisotope brain scans are procedures that should be performed at once if brain tumor is suspected.

Learning Disorder Syndromes

Developmental Hyperactivity, Minimal Brain Dysfunctions, Specific Learning Disabilities, Perceptual Deficits, Developmental Dyslexia

When the physician has completed the neurological examination and has disposed of the issues listed under Differential Diagnosis, the nature of the problem from a medical viewpoint becomes highly uncertain. A welter of psychometric data, family disturbances, educational theories, drug programs and "neurological" theories will confuse the most conscientious physician in the assessment of children with learning difficulties who do not have identifiable somatic problems. There is little agreement about the origin of learning difficulties that affect a substantial number of school-age children. A discussion of these issues will usually reflect the particular frame of reference of the discussant. Nevertheless, it is possible to make a number of statements about minimal brain dysfunction and related terms that may fairly represent the current situation:

- The acquisition of visual or auditory percep-

tual skills is determined by the interaction of genetic, cultural and familial factors that determine maturation in this field much as they determine maturation of motor, speech and social skills. The statement that a child has a "perceptual deficit" as determined by performance on highly structured psychometric tasks is essentially a restatement of the fact that a child is having learning difficulties. It tells little of the origin or nature of the deficit. It is essential to remember that many factors may affect a child's performance on psychological tests. Chief among these are inadequate motivation, emotional conflicts and limitations stemming from disadvantaged environments. The presence of evidence of perceptual deficits cannot be automatically attributed to cerebral dysfunction.

There is growing evidence that many children labelled as handicapped by perceptual disturbances really have a deficit of attentional abilities.[27] Other investigators have emphasized poor teaching practices as the basic problem when children of normal intelligence fail to learn at school. Socioeconomic and family factors play a significant role in determining achievement in the classroom. The term *specific learning disability* is a useful expression without etiological implications that can be used to categorize children with learning disorders who do not manifest any of the previously discussed illnesses.

• Hyperactive behavior (short attention span, distractibility, impulsivity are essentially equivalent terms) is a sign of behavioral disturbance that may be associated with a wide spectrum of syndromes. Mental retardation, brain damage syndromes, seizure disorders, primary behavior problems, overly restrictive environments, dysfunctional families, childhood autism and neurological degenerative disorders are all conditions that may result in hyperactive behaviors. The presence of this behavioral syndrome should alert the physician to carefully evaluate the child and his environment for the presence of these factors. Some children, otherwise quite normal or even precocious in development, manifest high activity levels as part of their temperamental characteristics. The term *developmental hyperactivity* has been applied to these children.[28]

• Most investigators who have studied the family status of children with learning disorders have recognized the prevalence of disturbed and dysfunctional families. This approach is not popular among educators at present but seems apparent to clinicians who see these children and their families.

• The presence of questionable, borderline or mild EEG abnormalities in children is not a reliable guide to the presence of cerebral dysfunction in children. Slow wave patterns in posterior regions, sporadic sharp waves, 14 and 6 cycle per second positive spikes and other EEG variants are common in normal children. Emerging information about the EEG in highly selected normal children[29] is providing new information about the wide range of normal variation in the EEG's of children.

• *Minimal brain dysfunction* as a nosological entity remains a poorly defined concept at present. It is essentially a diagnosis of exclusion in children with learning and behavioral problems after gross neurological, psychiatric and social causes of learning problems have been ruled out. Soft neurological signs are highly nonspecific findings that are affected by the same factors as those previously mentioned in discussing perceptual deficits. Attentional difficulties, memory difficulties, laterality disturbances, overflow movements, minor reflex asymmetries and other "subtle" signs of cerebral dysfunction are usually due to maturational lags, psychological stresses or both of these factors interacting. Macdonald Critchley's[30] concept of the dyslexic child as a "late bloomer" is more to the point in explaining the nature of many learning problems in children than is the notion of a cerebral dysfunction.

• The high incidence of learning disorders in boys remains an enigmatic phenomenon. Virtually all series analyzed reveal a striking male preponderance up to five to one. The peculiar predilection of boys to manifest learning problems has been attributed to various factors[31] but no really satisfactory explanation is available. The slower tempo pace of maturation in boys, the greater social expectation for achievement, an innate male aggressivity with poor impulse control, feminine dominance in grade-school and maternal difficulties with assertive behavior in their sons all have been considered. Perhaps each plays a role in specific cases.

• The tactics and strategy of managing a child with a learning disorder are more appropriately the task of a family-oriented physician than a neurological consultant. Perhaps this view might be restated that, insofar as the neurological consultant wishes to assist the child with a learning disorder beyond clarification of specific neurological issues, he must develop the attitudes of a

TABLE 1.—*Principles of Management of Learning Disorders*

1. Communicating a Diagnosis with Explanation of Terms—For Example, Hyperactivity, Specific Learning Disability, Dyslexia, Delayed Language Maturation, Minimal Brain Dysfunction.
2. Parent Counseling. Reordering environment of hyperactive children, consistency of routines, consideration of adverse family factors. Referral for psychological therapies such as behavior modification for the child or family therapy for parents.
3. Education Therapy. Use of individual tutors, special classes or special schools.
4. Drug Therapy. Use of Cerebral Stimulants (methylphenidate or amphetamines) in "hyperactive children." Avoidance of barbiturates or related drugs.
5. Continuous supervision for evaluation of success or failure of treatment programs.

physician aware of family and community processes. This will lead him far afield from neurological diagnosis but he will be fortified by recollecting that helping the patient in all aspects of his life is the oldest tradition of Hippocratic medicine. Furthermore, the neurological consultant is in a better position than other physicians or professional workers to integrate the various strands leading to a learning disorder and to guide the parents in evolving a sensible and unbiased approach toward the problem.

The purpose of this review is not a detailed discussion of the role of the physician in the management of children with learning disorders. However, it may be appropriate to indicate general categories of management approaches. These are summarized in Table 1. Further consideration of management issues can be found elsewhere.[1]

Conclusion

The prevalence of children with learning disorders in our society means that physicians who treat children must develop a point of view and a working procedure for assisting children brought to them with the principal complaint of difficulties in school. An approach to this problem can be divided into two parts: (1) detection of specific neurological or sensory disorders and (2) comprehensive management of school problems. The detection of neurological disorders relies upon conventional medical knowledge for recognition and treatment of disease states that may have produced or significantly contributed to the school problem. Comprehensive management requires a broader approach by the physician, including parent counseling, advice about educational issues and consideration of drug therapy. In all instances, parents should be able to rely on the physician to act as a scientific resource for guidance as to merits of various kinds of therapy directed toward children with learning disorders. The ability to function effectively in this manner will enable the physician to provide a service to children and their families that may profoundly affect their lives.

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Refer to: Isolated hypoaldosteronism—Medical Staff Conference, University of California, San Francisco. Calif Med 118: 33-38, June 1973

Medical Staff Conference

Isolated Hypoaldosteronism

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* *As all of you know, there has been great interest in conditions associated with excessive secretion of aldosterone both as a primary event in the pathogenesis of hypertension and as a secondary phenomenon in conditions associated with edema states. The topic today, however, will be hypoaldosteronism as an isolated defect. The case summary of a patient with such a defect will be given by Dr. Lynn Tamsky.*

DR. TAMSKY:† The patient is a 73-year-old black man who was admitted here in January 1973 for further study of his renal acidification mechanisms. In August 1972 he was first admitted to the San Francisco General Hospital where he was found to have hypertension, mild azotemia, and persistent hyperkalemia. On subsequent clinic visits, his serum potassium was consistently greater than 6 mEq per liter, and at one point he was given a brief trial of a cation exchange resin which resulted in edema and increased blood pressure. His serum potassium remained elevated and in October 1972 it was 7.2 mEq per liter; he was then readmitted to San Francisco General Hospital for treatment of hyperkalemia. On that admission, he gave a history of eating 10 to 15 bananas a day, as well as other fruit. Consequently, at that stage, he was believed to have hyperkalemia secondary to the elevated amount of potassium in his diet in the face of chronic renal failure, and a potassium restricted diet was prescribed. Additional laboratory data included creatinine of 3.0 mg and blood urea nitrogen (BUN) of 50 mg per 100 ml, creatinine clearance of 28 ml per minute, and serum bicarbonate of 21 mEq per liter. Despite two weeks of low potassium intake, the serum potassium remained above 6 mEq per liter, which was considered to be too high for his degree of renal failure. A diagnosis of hypoaldosteronism was established by demonstration of subnormal renin and aldosterone levels during sodium restriction. These studies will be discussed in detail by Dr. Schambelan.

On December 2 1972 he was admitted to the University of California Medical Center for evaluation of renal acidification mechanisms. Electro-

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†Lynn Tamsky, MD, Resident in Medicine.

lyte values on admission were: Sodium 135 mEq, potassium 6.8 mEq, and chloride 107 mEq and carbon dioxide content 23.4 mEq per liter. Arterial pH was 7.38, carbon dioxide partial pressure (pCO_2) 29.8 mm of mercury and bicarbonate 17.5 mEq per liter. While the patient was in the hospital administration of 9 α-fluorohydrocortisone was begun, 0.1 mg daily, as replacement for the mineralocorticoid deficiency. At first there was a slight worsening of acidosis, with a fall in carbon dioxide content to 20 mEq per liter and a fall in arterial pH to 7.34. Therefore, on discharge from the hospital supplemental sodium bicarbonate was prescribed.

The patient was readmitted to this hospital January 2 1973. Blood pressure was 170/90 mm of mercury, and vital signs were otherwise normal. In general the patient was oriented and alert, but he did have a very poor memory and was unable to give much history. He had bilateral cataracts, and arteriovenous nicking was noted in the fundi. The chest was clear to auscultation. A grade 2/6 systolic ejection murmur was noted. Pedal pulses were absent. Abdominal and neurological examinations were normal. Electrolyte values on this admission showed carbon dioxide content of 34 millimoles per liter and arterial pH of 7.44. The bicarbonate supplement was stopped. Carbon dioxide content fell to 26 millimoles per liter and the arterial pH to 7.39 and the patient was discharged with a prescription of 9 α-fluorohydrocortisone, 0.15 mg per day, along with sodium chloride supplements.

DR. SMITH: *We have asked Dr. Morris Schambelan to open the discussion on this particular problem. Dr. Schambelan is from the Division of Endocrinology at the San Francisco General Hospital and, as most of you know, has had a long interest in the area of mineralocorticoid metabolism in health and disease. Morris, what is hypoaldosteronism and how can we recognize it as an isolated defect?*

DR. SCHAMBELAN:* Thank you, Dr. Smith. I would like to begin with a brief review of the clinical problem of hyperkalemia, then to deal in detail with the entity of isolated aldosterone deficiency, particularly our studies regarding its mechanism and, finally, to review the studies performed in the patient presented today.

*Morris Schambelan, MD, Assistant Professor, Department of Medicine, San Francisco General Hospital.

In approaching a patient with hyperkalemia, one is usually initially concerned with the state of renal function. We are all familiar with the fact that in acute renal failure hyperkalemia is a major clinical problem. In the face of a pronounced reduction in urinary flow-rate, the potassium load from dietary and catabolic sources frequently results in a dangerous elevation of serum potassium which may require emergency dialysis. This is particularly true when patients have been subjected to severe trauma with muscle breakdown and a further increase in the potassium load. By contrast, in the majority of patients with chronic renal failure, hyperkalemia is not a serious problem. It has been observed for many years that most patients with stable chonic renal disease have a normal or perhaps only slightly elevated serum potassium.[1] With reduction of urinary flow-rate, particularly in the oliguric end-stage, hyperkalemia often becomes manifest. Hyperkalemia may also occur in patients with otherwise stable chronic renal failure in whom extracellular fluid volume is transiently reduced as a result of vomiting or use of large doses of diuretics.

An important question to consider in the patient under discussion today, who had only moderate azotemia, was whether his high potassium intake, particularly the bananas, could have contributed to his hyperkalemia. The average medium sized banana contains between 18 and 20 mEq of potassium and he was eating 10 to 15 of them daily, plus a variety of citrus fruits. A normal person can adapt very well to a large potassium intake and there are older studies in which people who subsisted largely on potatoes were shown to tolerate up to 1,000 mEq of potassium daily without difficulty.[2] In subsequent studies where serum potassium measurements were available, the chronic administration of 500 mEq of potassium daily to patients with normal renal function was not associated with hyperkalemia.[3] Clearly, patients with renal disease have an impaired ability to excrete potassium acutely,[4] but these patients generally adapt well to chronic potassium loads. Our patient entered the hospital with potassium of 7.2 mEq per liter and after two weeks of a low potassium diet was still significantly hyperkalemic. It was thought, therefore, that dietary intake alone did not account for hyperkalemia in his case.

Additional causes of hyperkalemia must also be considered. Extracellular fluid acidosis can result in an increase in the concentration of serum

potassium despite total body potassium depletion. In severe diabetic ketoacidosis we frequently see patients with elevation of serum potassium when the arterial pH is 6.9 or 7.0, but frank hypokalemia becomes apparent when the acidosis is corrected. Drugs, particularly spironolactone and triamterene, are now part of many combination diuretic agents and always must be considered in a patient who has hyperkalemia. Spironolactone appears to work by competing with aldosterone at its receptor site, while triamterene has an action that is independent of the mineralocorticoid. Either can cause an increase in the serum potassium levels. Finally we must consider the possibility of "pseudohyperkalemia," which can occur in patients with pronounced increase in platelet counts and in essence represents an artifact of blood coagulation with lysis of platelets and release of potassium into the serum. Circulating potassium levels are normal and may be demonstrated by asking the laboratory to measure plasma as well as serum electrolytes.

Since none of the previously mentioned causes of hyperkalemia appears to apply to our patient, we must turn to a consideration of a deficiency of mineralocorticoid hormone. Classically, that can occur as part of a generalized adrenocortical disorder as in Addison's disease or as a rather specific defect in aldosterone production, which brings us to the topic of this morning's discussion.

So-called isolated hypoaldosteronism has been recognized for about 15 years. The first example was described by Hudson et al in 1957,[5] in an elderly patient who presented with Stokes-Adams attacks. The patient was found to be hyperkalemic, and subsequent evaluation demonstrated an impairment in aldosterone production. However, this appeared to be an isolated adrenocortical defect, since cortisol production was normal and responded normally to adrenocorticotropic hormone (ACTH). Small doses of a mineralocorticoid hormone corrected the hyperkalemia and reversed the entire syndrome. Since that time, approximately a dozen patients have been described who appear to have had a similar abnormality with the classical clinical feature being hyperkalemia, whereas the cardiac conduction abnormalities have not been present in all patients. These patients are distinguishable from those with Addison's disease by demonstrating impaired aldosterone production and normal production of the glucocorticoid hormone, cortisol. The mechanism for this disorder has not been clearly defined. It is known that some infants may have a defect in the later stages of aldosterone biosynthesis which can result in impaired production of aldosterone but not the other adrenal products.[6,7] However, in most of the adult patients who have been studied, there has been no solid evidence of an enzymatic defect.

We became interested in this disorder about three years ago when such a patient was studied at San Francisco General Hospital. Since that time we have been able to identify about 20 patients with this disorder, which suggests that this may be a common syndrome. We have recently published data on our first six patients[8] and at present have completed studies of 14 patients. All have been adults in the age range 40 to 80 years, with a preponderance of males. The presenting clinical abnormality in all the patients was hyperkalemia, usually discovered as part of routine laboratory testing. One patient presented with complete heart block, but the majority of our patients have been asymptomatic. Most of the patients do not have significant hyponatremia, although sodium conservation is usually not normal. Two of the patients in our original study group had hyperchloremic acidosis, and some degree of metabolic acidosis has been present in the majority of the patients. Renal function was reduced in all patients but usually not to a severe degree, with creatinine clearances ranging from 18 to 72 ml per minute, the average being around 40 ml per minute. A variety of associated diseases were noted that may have some role in the production of this syndrome, including diabetes mellitus, pyelonephritis, previously treated hyperparathyroidism, gout, and, in one of the patients, an aldosterone-producing adenoma that had been removed five years previously. This latter patient never regained normal production of aldosterone from her remaining adrenal gland.

After excluding the causes of hyperkalemia discussed earlier we proceeded to evaluate the patients for generalized adrenocortical insufficiency. ACTH was given for three days and urinary steroid excretion in response to this stimulus was measured (Chart 1). Urinary 17-hydroxycorticoids increased from a normal baseline in a brisk and sustained manner, which excluded the diagnosis of generalized adrenal insufficiency. Urinary aldosterone excretion was subnormal and did not increase significantly in response to ACTH. The possibility of enzymatic defect was considered, since, as I mentioned earlier, examples of isolated aldosterone deficiency have been described in infants in

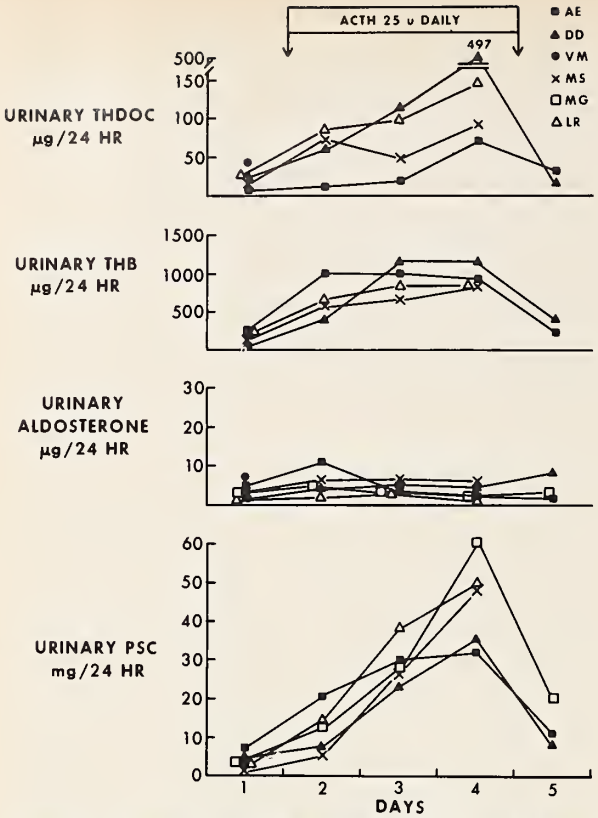


Chart 1.—Effect of ACTH administration on the urinary excretion of tetrahydrodeoxycorticosterone (THDOC), tetrahydrocorticosterone (THB), aldosterone, and 17-hydroxycorticosteroids (PSC) in five patients with isolated hypoaldosteronism. (Reproduced with permission from New Engl J Med, reference 8.)

whom a defect in the 18-hydroxylation of corticosterone or the subsequent dehydrogenation to aldosterone was noted. Since these enzymatic steps are not required in the biosynthesis of cortisol, the defect is restricted to aldosterone production. An 18-hydroxylation defect seemed unlikely in our patients, since excretion of metabolites of deoxycorticosterone and corticosterone was normal, as distinguished from the elevated levels noted by Visser and Cost in their patients with this syndrome.[6] Similarly, an 18-dehydrogenation defect was excluded by demonstration of low or normal excretion of 18-hydroxy compound A. These values were determined for us by Dr. Stanley Ulick. Furthermore, in our patients the ratio of this metabolite to tetrahydro-aldosterone was normal, in contrast to the markedly elevated ratio observed by Dr. Ulick in his patients with an 18-dehydrogenation block.[7] We felt, therefore, that both generalized adrenal insufficiency and an enzymatic block had been excluded in our patients.

The presence of a severe deficiency in aldosterone production was more appropriately demonstrated by evaluating the response to a five- to seven-day period of sodium restriction (Chart 2). Patients were initially equilibrated on a 120 mEq sodium intake daily and then dietary sodium was reduced to 20 mEq daily. The normal range for aldosterone execretion on a 120 mEq diet is 4 to 17 micrograms per 24 hours and 20 to 67 on the salt-restricted intake. The baseline production of the hormone was either frankly subnormal or at the lower limit of normal in all patients, and while there was some increase in response to salt restriction, in none of the patients did the levels reach those found in normal subjects. In addition, plasma aldosterone levels were subnormal on the normal sodium diet and also failed to increase normally during salt restriction.

In the absence of evidence of a primary adrenal abnormality, we decided to evaluate the renin-angiotensin system, since this is the principal regulator of aldosterone production in man. Using a radioimmunoassay technique, we found that plasma renin activity was clearly subnormal in both supine and upright positions during the control and salt restriction dietary periods (Chart 3). For a further determination of the stimulus to renin, we evaluated the effect of acute administration of furosemide at the completion of the salt restriction period with patients upright for four hours, and found no further increase in the subnormal values. To exclude an abnormality in renin substrate, we measured plasma renin concentration by adding excess substrate to the reaction mixture and again saw frankly subnormal values. In several of the patients, we directly assayed substrate concentration by adding an excess of renin to plasma and found that the renin substrate levels were normal or perhaps somewhat increased. The evidence indicates that in these patients the enzyme renin is subnormal.

The subnormal renin levels were a bit surprising, since one would expect a patient with aldosterone deficiency, who would be subject to sodium wasting and extracellular fluid depletion, to have elevated renin levels. In fact, patients with Addison's disease have been observed to have decidedly elevated renin levels.[9] We decided to examine this question ourselves in several patients with generalized adrenocortical insufficiency. The patients were given dexamethasone so that we could study the effect of an isolated mineralocorticoid deficiency, and they underwent a period of salt restriction as

had the previous patients. As had been expected, there was no increase in urinary aldosterone, yet plasma renin levels were greatly elevated. When the renin levels are compared directly with those of the patients with isolated hypoaldosteronism, the difference is in the range of 50- to 100-fold. This wide disparity between the high levels of renin that one might anticipate in the face of mineralocorticoid deficiency and the low levels seen in the patients with the isolated defect has led us to suggest a primary renin deficiency mechanism for this syndrome.

The patient presented today was studied under a similar protocol. Initially he received ACTH for three days and the response of aldosterone and cortisol was evaluated. The baseline 17-hydroxy-

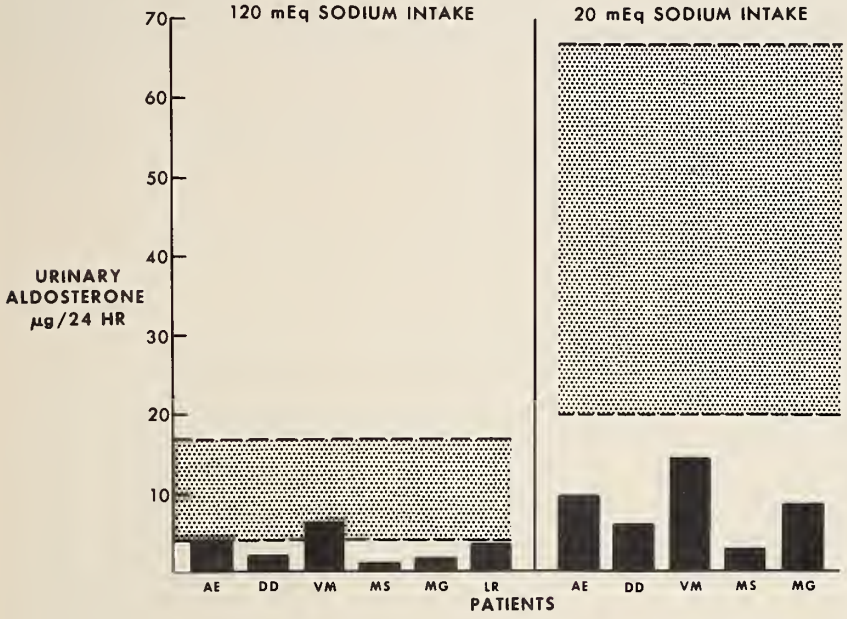


Chart 2.—Urinary excretion of aldosterone in six patients with isolated hypoaldosteronism during normal and low sodium intakes. Sodium restriction was not performed in one patient (LR). Ranges for normal subjects are indicated by the stippled areas. (Reproduced with permission from New Engl J Med, reference 8.)

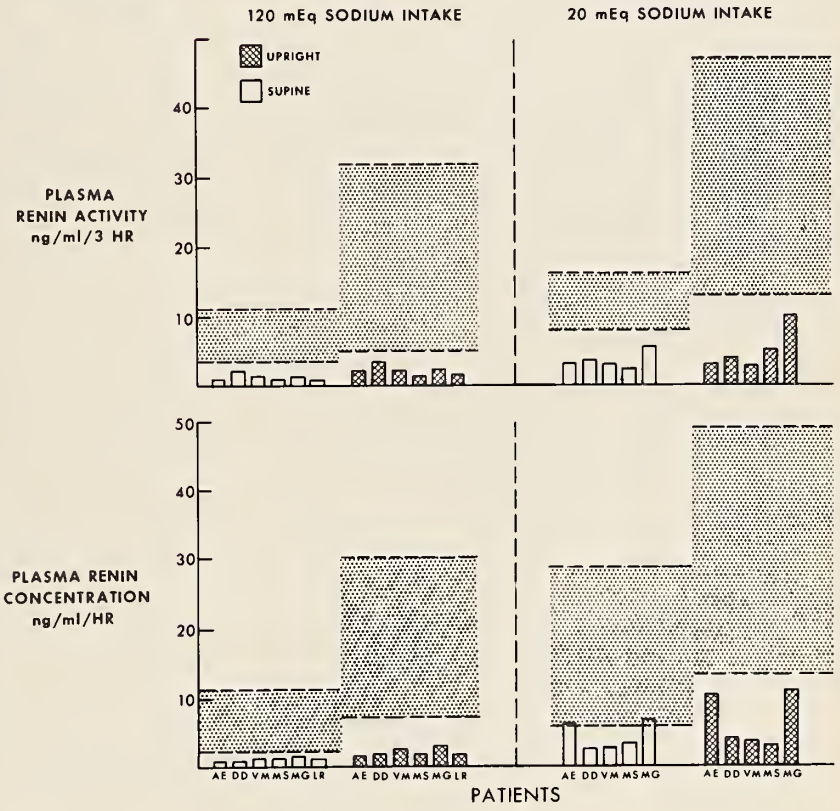


Chart 3.—Plasma renin activity and concentration in six patients with isolated hypoaldosteronism during normal and low sodium intakes and the effects thereon of supine and upright posture. Sodium restriction was not performed in patient six. Ranges for normal subjects are indicated by the stippled areas. (Reproduced with permission from New Engl J Med, reference 8.)

corticoids were 5.9 mg per 24 hours and in response to ACTH there was a brisk and sustained increase up to ten times the control value. The control urinary aldosterone excretion was 3.1 micrograms per 24 hours which is below our normal range of 4 to 17 and, except for a very minor increase, it remained essentially unchanged during ACTH administration. When a low sodium diet was given, the patient had a 350 mEq negative sodium balance over a six-day period. The urinary aldosterone excretion on the control day was 2.4 μg per 24 hours and increased only minimally to 5.3 μg by the fifth day of salt restriction. Similarly, plasma aldosterone levels were subnormal under these same study conditions. Basal plasma renin activity was 3.2 nanograms per 100 ml per three hours, with no increase in response to upright posture and only a very slight increase with the other stimuli of sodium restriction and intravenous furosemide. So today's patient fits the picture that we see in patients with isolated hypoaldosteronism.

Time does not permit a detailed review of the studies of a renal acidification which were performed during this patient's stay in hospital here, other than to note that in collaboration with Drs. Anthony Sebastian and R. Curtis Morris we have been evaluating the role of aldosterone deficiency in the hyperchloremic acidosis seen in so many of these patients. The preliminary data would suggest that mineralocorticoid replacement may partially correct the acidosis, but I will leave a full discussion of this aspect of the problem to a later date.

One further comment seems indicated. While our studies have suggested that a primary abnormality of renin secretion may underlie isolated hypoaldosteronism in adults, we have not as yet defined the pathogenesis of the renin deficiency. The frequency with which we have seen associated diseases such as diabetes, pyelonephritis and gout suggests that the impairment in juxtaglomerular cell function may occur as an acquired defect in the course of these diseases. These are common diseases, and our studies suggest that isolated hypoaldosteronism may be a relatively common syndrome. Since administration of small doses of mineralocorticoid hormone easily corrects the hyperkalemia, this diagnosis should be considered in any patient with otherwise unexplained hyperkalemia.

DR. SMITH: *Thank you, Dr. Schambelan.*

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Important Advances in Clinical Medicine

Epitomes of Progress—General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in General and Family Practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in General and Family Practice which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

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Treatment of Streptococcal Pharyngitis by Clinical Criteria

CLINICAL CRITERIA CAN BE USED to diagnose and treat pharyngitis without a culture if the effects of age and causative agent are considered.

Studies have shown that accuracy of clinical diagnosis averages 75 to 80 percent. However, within this average, there are areas of extremely high accuracy. A study to be published shows that accuracy is 97 percent when a clinical diagnosis of viral pharyngitis is made in an adult. Accuracy fell to 41 percent when a clinical diagnosis of streptococcal pharyngitis was made in a child. Unfortunately the studies which attack clinical diagnosis are usually by pediatricians.

Adenitis and exudate are the two most important criteria in making a clinical diagnosis. Temperature and injection are less important. Viral pharyngitis is diagnosed if all of these findings are absent or if temperature alone is present along with typical influenza symptoms. Streptococcal pharyngitis should be diagnosed only in the presence of (1) marked exudate (without signs of mononucleosis), (2) marked erythema, (3) a combination of adenitis, temperature, and moderate injection or exudate.

Between the viral and the streptococcal categories are patients with unexplained temperature, adenitis, minimal injection, or minimal exudate along with their pharyngitis. These should be placed in a questionable category and cultures taken before treatment.

For adults with a clinical diagnosis of viral pharyngitis, cultures should not be done. The incidence of rheumatic fever will be only 1 in 8,000 if clinical diagnosis rather than laboratory diagnosis is used. Cultures would be an inefficient use of health dollars.

Children diagnosed clinically as having viral pharyngitis should have cultures even though accuracy is a relatively high 86 percent, since their risk of rheumatic fever is much greater.

It is generally agreed that patients given a clinical diagnosis of streptococcal pharyngitis should be treated before culture results are available to

minimize the possibility of rheumatic fever. Clinical accuracy in the previously mentioned series was approximately 70 percent for adults and 40 percent for children. This is high enough to justify immediate therapy without culture for adults, provided it is oral and the danger of anaphylaxis is avoided.

Penicillin injections in children are not justified because of the inaccuracy of clinical diagnosis and the danger of delayed sensitivity in later life. However, the greater incidence of rheumatic fever in children suggests that oral therapy should be started pending culture. Studies have shown that eradication of steptococcal infection is excellent by oral therapy if proper instruction is given to the patient.

By following these criteria, over 70 percent of cultures can be eliminated. A majority of clinicians already treat on the basis of clinical judgment. By adhering to standard criteria and taking cultures in pediatric pharyngitis and questionable cases in adults, the cost of medical care can be reduced without danger.

ROGER A. FORSYTH, MD

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Pain in Viral vs. Bacterial Pharyngitis

IT IS GENERALLY ACCEPTED that streptococcal pharyngitis cannot be diagnosed from clinical findings alone without significant error.

Since the two commonest bacterial organisms responsible for acute pharyngitis are the group A streptococcus and C. diphtheriae, and since the latter can usually be excluded on clinical grounds, the physician must ask, when he makes the diagnosis of pharyngitis, whether it is caused by group A streptococcus or by a virus. The diagnosis of pharyngitis is often made on the basis of the complaint of "sore throat" without definite signs of redness, exudate or ulceration of the pharynx.

In any general practice the problem of differentiating viral from bacterial pharyngitis is a daily problem. Much has been made of the "beefy" pharyngitis so often typical of streptococcal sore throat, but another aid to differentiation can be made from the history.

As a general rule, pharyngeal pain which occurs primarily or is most severe at bedtime and on arising may help to differentiate viral from bacterial sore throat. The latter tends to be more or less constant throughout the patient's waking hours. With a history of persistent daytime pharyngeal soreness, it is desirable to obtain a throat culture, even though the pharynx is not inflamed. In these patients an occasional unexpected hemolytic streptococcus infection will be discovered.

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Office Dilatation and Curettage

ALTHOUGH METHODS of endometrial sampling have been present for approximately fifty years, there has been relatively little acceptance of any but the traditional dilatation and curettage. Adequate diagnostic D & C can be done in the office with the Poyas cannula. The equipment needed consists of three cervical dilators and matching cannula curettes, tubing with a specimen trap, and low pressure suction pump commonly used in most offices. The stainless steel cannula curettes are 12 inches long, with a 4, 5, or 6 mm outside diameter. The tips are straightened to produce the effect of a sharp curette and the shaft is slightly curved to allow free rotation and contact with the uterine wall.

The procedure is carried out much as the traditional D & C, with a careful bimanual examination beforehand to determine uterine size, shape and position. Visualization can be improved with a weighted speculum. The cervix is then grasped with a single tooth tenaculum and cleansed. Depth is determined with the introduction of the 4 mm dilator and most cervical canals can then be dilated to the large (6 mm) diameter. If the dilatation is uncomfortable for the patient, a paracervical block using 5 cc of 1 percent lidocaine (Xylocaine®) at the 4 and 8 o'clock positions will afford adequate relief. Thorough curettage can then be carried out, and the removed tissue aspirated into the trap. The tubing can be cleared at the end of the procedure with a small amount of formalin and the specimen sent to the laboratory. Even very scanty specimens will be adequate for pathological diagnosis if a "cell block" is asked for.

Where this suction procedure has been done and the conventional method and/or hysterectomy

carried out later, it has been found there is little, if any, endometrial tissue remaining. Most small polyps will be removed and larger ones can be felt. The cannula curette thus offers a diagnostic office procedure which relieves the patient of the risk and cost of hospitalization for a traditional D & C under general anesthesia.

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Cryocautery in the Office Treatment of Chronic Cervicitis

A SIMPLE AND EFFECTIVE office technique for managing chronic cervicitis or cervical erosion—conditions which often are accompanied by a mild but chronic vaginal discharge that is not abated by treatment with various vaginal creams over a long time, with many office visits.

After a Papanicolau smear has been obtained and found to be normal, the patient is ready for definitive treatment with cryocautery. Generally, no premedication is necessary but relaxation with 10 mg of diazepam (Valium®) and 0.5 mg of atropine to control parasympathetic response is recommended by some observers. The cryocautery is applied to the cervix for 2 to 3 minutes when Freon® or carbon dioxide is the cooling agent. The margin of freezing can be visualized and is usually carried 2 or 3 mm beyond the area of the erosion. Some patients may feel some discomfort at the time of the procedure and for up to three days afterward. The discomfort is described as similar to menstrual cramps and is sometimes accompanied by light-headedness.

Following cryocauterization there is a clear, watery discharge for nearly two weeks, followed by a mucoid secretion. Intercourse is not advised for two weeks. Some patients have spotting. At the end of six weeks, the cervix is usually healed. The procedure apparently does not cause cervical stenosis that might have adverse effect on subsequent pregnancy. Some observers have reported that dysplasia of the cervix has disappeared following cryocautery treatment.

JOHN F. BRIDGEMAN, MD

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Minor Tranquilizers—How Minor Are They?

IN THE MID-1950s the alkaloids of rauwolfia serpentina were introduced into this country. They had been used for centuries in the Far East. Their sedative action was characterized as tranquilization. This label has since been applied to a wide variety of other compounds with sedative effects. Each is introduced with some enthusiastic reports of clinical trials and some well-financed sales-promotion propaganda. Objective evidence of selective "transquilization" as against sedation has been almost nonexistent. By 1960 it was evident that reserpine could produce profound depression and a substantial number of suicides were attributed to its use either as a tranquilizer or in the treatment of hypertension.

Meprobamate appeared next on the scene and was hailed as an effective treatment for anxiety, safe and free from side effects. Its profound hypnotic effects were largely ignored or played down. Habituation to meprobamate was soon reported and, more startling, seizures, often fatal, were reported upon withdrawal of meprobamate from addicted persons. Again depression was a common side effect. Widely heralded muscle-relaxant properties have found little application.

The chlordiazepoxide compounds, with chlordiazepoxide (Librium®) as the first entrant, boomed to the top of the sales list in the 1960s. With this class of "tranquilizers" it was possible to demonstrate in experimental animals some difference in behavioral effects between the benzodiazepine compounds on the one hand and meprobamate and barbiturate on the other. Both chlordiazepoxide (Librium®) and diazepam (Valium®) are capable of abolishing spastic rigidity in decerebrate cats. Diazepam (Valium®) is more potent as a muscle-relaxant than Librium®. Intramuscularly administered diazepam has gained acceptance as a treatment of status epilepticus.

Physical dependence on chlordiazepoxide or diazepam resembles that seen with barbiturates and meprobamate. Patients receiving large doses for several months have experienced withdrawal symptoms within a few days. Two of ten patients had seizures a week after discontinuance; other symptoms following withdrawal were depression, agitation, insomnia, loss of appetite and aggravation of the preexisting psychopathological state.

Patients are very resistant to withdrawal of "minor tranquilizers" even though the physician

readily detects the signs and symptoms of central nervous system depression, drowsiness, lethargy, depressed mood and decreased function.

J. Blair Pace, MD

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Can the Diaphragm Make a Comeback?

The raging venereal disease epidemic, which gains momentum year after year, will not be controlled, we are told by public health authorities, by treatment, but only by prevention. Since a satisfactory immunization for gonorrhea or syphilis seems a good many years away, we must review the facilities that are at hand. The incidence of venereal disease in younger age groups has increased. The 9-to-12-year age group is now affected. It appears that persons growing up in the United States today would have a 50/50 chance of having gonorrhea between the ages of 12 and 25. "The pill," besides removing fear of conception as a deterrent to sexual activity, contributes in another and very substantial way to the incidence and transfer of gonorrheal infection. By increasing the glycogen content of the vaginal cells and by increasing the mucous secretion of the cervical glands, the pill produces an ideal soil for the growth of the gonococcus. It thus appears that if the female has sexual contact with a gonorrhea-infected male and she is taking the pill, she is almost certain to acquire the disease. The same female not taking the pill and having the same single contact with the same male would have perhaps a 40 percent chance of contracting the disease.

It is not known what additional reduction might occur in the incidence of infection if this same person were not only off the pill but were also using a diaphragm with a jelly or cream which contained not only contraceptive but also bactericidal agents.

It is not at all difficult to conceive that our large pharmaceutical firms could readily develop a compound that is both spermicidal and bactericidal against the gonococcus or perhaps a large variety of venereal infections including syphilis. Progonasyl, a product long on the market but not approved for venereal disease prophylaxis, has been suggested for this very purpose by a California Medicine contributor.

Conscientiously used, a diaphragm used with a contraceptive cream or jelly is 95 percent effective in contraception. This compares favorably with the contraceptive effectiveness of the intrauterine device.

If an educational campaign could be launched which would emphasize the safety, effectiveness, and the venereal disease protective value of the diaphragm with cream or jelly, this almost abandoned modality might make a comeback.

J. Blair Pace, MD

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Prophylaxis of Migraine Using Propranolol

Fortuitous observation of improvement in migraine—or prevention of migraine attacks—came from various centers almost simultaneously. Several of the patients who were taking propranolol for cardiac indications were migrainous physicians.

Follow-up controlled studies using placebo and a double-blind technique indicated over 75 percent good to excellent response to the administration of propranolol in dosages in the order of 20 mg four times daily. Side effects can be expected in less than 2 percent of patients on this therapy if the known contraindications are observed. Known contraindications include asthma, diabetes mellitus and cardiac conditions where diminished cardiac output would produce problems.

Propranolol is a beta-adrenergic receptor blocker. Precise rationale for its use in migraine has not been fully developed. The most evident mechanism is blockade of vasodilator receptors in adrenergically innervated vessels.

The author recently observed an atypical migraine sufferer, a 34-year-old man, who described his attacks as characterized by flushing of the face and the head. Frequency and severity of attacks was reduced more than 50 percent by propranolol.

Propranolol is not yet the established treatment of choice in all migraine patients. Where more

traditional prophylactic measures have failed, a trial of propranolol is worthwhile.

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Lactase Deficiency, Geriatric and Ethnic Considerations

Milk has long been looked upon almost reverently as the perfect food. Almost 50 percent of the caloric value of breast milk is accounted for by the lactose content. Specific lactase deficiency in the newborn often produces symptoms after the first few feedings. This probably has a congenital hereditary basis.

A very high lactase level in the newborn is not usually maintained into adult life. Adequate lactase production may occur into the fifth and sixth decades in persons of Scandanavian background. Other racial groups develop lactase deficiency early in life. Specific lactase deficiency has a very high incidence in American Negroes. This deficiency appearing early in life is also common in India and in Greek Cypriots, Arabs and Ashkenazi Jews.

There is a quantitative aspect to lactase deficiency. In our own society the quantity of milk intake by adults may not be high enough to give rise to symptoms until the patient is put on frequent feedings for treatment of peptic disease. Most of these feedings involve a great deal of milk. In geriatric practice it is safe to assume that patients complaining of functional distress, gas, cramps, flatulence and at times diarrhea, alternating with constipation, may be greatly benefited by removing milk from the diet.

It has not been established whether or not specific lactase deficiency is an important aspect of the aggravation of regional enteritis by milk. The specific tests for lactase deficiency are less satisfactory than indirect tests. Three weeks of careful milk-free diet followed by a milk challenge, which produces symptoms, is a valid test. In infants evidence of conversion of lactose to glucose, following a lactose test meal, is a valid test of the adequacy of lactase production.

Aside from being iron-deficient, milk is far from a perfect food for persons who suffer from specific lactase deficiency or from specific milk protein allergy. The specific lactase deficiency problem has both age and ethnic group relationships.

J. Blair Pace, MD

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Hypothyroidism—Do We Finally Have a Single Test?

Advances in method have made the radioimmunoassay of human thyrotropin (TSH) available to the physician in practice for diagnosis of hypothyroidism. The normal ranges of TSH by this method have been defined. It may be assumed that elevated levels of TSH are a sensitive index of primary hypothyroidism. In fact TSH is a more sensitive index of thyroid damage than the level of circulating hormone. Conversely, normal levels of TSH allow one to confidently exclude the diagnosis of hypothroidism.

James R. Wheat, MD

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EDITORIAL

Training for Research in Medicine

—*A Change in National Policy*

During the past 25 years biomedical research has been remarkably expanded in the United States, largely because of increasing federal support. At the present time the Federal Government, predominately through the National Institutes of Health, supplies more than 60 percent of the estimated 2.7 billion dollars invested annually in biomedical research. A revolution in modern biology and in medical science has resulted. The success of this national policy can be measured in the major advances which have occurred in molecular biology, immunology, virology, pharmacology and genetics, and in the application of these and other disciplines to the prevention and treatment of disease. It is this policy which has made biology the most exciting science in the second half of the twentieth century, occupying the special position held by physics during the first half. More important, it allows for a rational approach to the major health care problem in the United States—that is, the continued existence of major diseases for which we can do little at present.

Excellence in research does not automatically follow the flow of funds into a field. It requires the selection and training of the comparatively small number of scientists capable of unusual research creativity. In recognition of this fact the Federal Government has supported the training of biomedical scientists in parallel with its investment in direct support of research itself over the past 20 years. This support has been largely through the instruments of training grants, established in those basic science or clinical departments judged to be outstanding by peer review, and through fellowships, given directly to the trainee. That policy is now being abruptly discontinued. The President's budget calls for cessation of federal support for research training, with the phase-out to be completed within the next few years.

What lies behind this decision and what consequences are likely to flow from it? The proximate cause is the laudable desire to reduce federal spending, and the amounts invested in training (approximately $180 million in training grants and fellowships in fiscal 1973) are not inconsequential. Even in deflated 1973 dollars this investment is above the noise level in the federal budgetary process. On the other hand, investment in cancer research and in research in heart disease is being simultaneously increased, so there is some selectivity in the elimination of support of training in the biomedical research budget. Some in the executive branch of government argue that there are enough scientists for anticipated future needs. Furthermore, education represents a certain equity for the recipient and he should make this initial investment from personal resources. In other words, no special incentive of training support is required. Moreover, in this view, reliance should be placed on the normal pull of market forces to produce the number, variety, and quality of biomedical scientists necessary for our future research effort.

The training grants and fellowships have not only supported those destined for a research career. They have also underwritten much and in some areas most of the specialty training in clinical disciplines—cardiology, gastroenterology, nephrology, neurology, and psychiatry, for example. The new budgetary decisions will sharply reduce the opportunity for such training in the United States, unless alternate means of support are identified. The bed-costs in teaching hospitals cannot absorb this additional fiscal burden, since they are already strained in the support of intern and resident stipends. Few young physicians can afford two or three additional years of training without stipend support as an addendum to normal residency requirements. The result will be decreased attractiveness for a research career and for science-based specialty training. In part, perhaps, this is the purpose of the legislation.

Is such a change in policy in the public interest? It is clear that the decision to discontinue federal investment in research training will be severely disruptive to medical education. The nation's medical schools are just beginning to assess the

impact in loss of operating budgets and in threat to educational programs. More important are the implications for the future of biomedical research. As noted earlier, the major health care problem of our time is the continued existence of diseases for which we do not have adequate measures for prevention or treatment. Even if we had a perfect system for distribution of health services, rheumatoid arthritis, schizophrenia, cancer, and coronary artery heart disease would remain as major threats to health. The only rational approach to finding answers to these and other diseases, which ultimately kill us all, is through medical research. Research in the biomedical sciences is therefore a form of national defense. Only a small number of medical school graduates, approximately 5 percent, enter careers of medical research. The national policy of the past 25 years—that of investing both in scientists as well as science—has created a magnificent organization or instrument for research in the United States. The decision to discontinue the policies which have brought us to our current successes seems both shortsighted and unwise. There is an immense opportunity to apply advances in biology to the elucidation of disease processes during the last quarter of the twentieth century. This opportunity should not be lost through cancellations of a successful program of training the required medical scientists.

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Proof of Effectiveness in Health Care

PROOF OF EFFECTIVENESS is a well-established concept in medical science. It is the goal of much research in the scientific aspects of medical care. Its application in medical practice and in other aspects of health care is less well-established but there are hopeful signs that this will occur. It is tempting to believe that this will be because the objectivity of science is winning greater acceptance on the basis of its inherent rationality in an irrational world, but it is far more likely that the really compelling reason is costs. The dollars available for health care are limited and more of them should be used where there is proof of effectiveness and fewer where there is not. A beginning is to be seen in the attempts of the Federal Food and Drug Administration to relate the availability and use of drugs and pharmaceuticals more closely to proof of their effectiveness, and it is easy to foresee proof of effectiveness playing a larger and larger role in the work of the federally mandated Professional Standards Review Organizations (PSRO's). In a sense the growing public concern that health professionals show evidence of their continuing competence may be viewed as another expression of the trend to proof of effectiveness. All of this is healthy and, if done well, will go a long way to achieve the seemingly paradoxical aims of improving the quality and reducing the costs of medical care at the same time.

The concept of proof of effectiveness strikes right to the heart of many of the scientific and social problems in health care. Much of the science and much more of the sociology, the economics and the politics of health care are dominated by widely held professional or public opinion, belief or even custom for which there is precious little proof of effectiveness. Many of these widely accepted views are of long standing and may have some basis in the human experience, but others in fact have been created artificially by the overstating and overselling of medical progress and by skillful public relations techniques designed to instill a habit or belief into public opinion or public behavior for whatever purposes. It is certainly timely and perhaps even overdue that many of these professional and public opinions, beliefs and practices be challenged for proof of their effectiveness in health care. This is beginning to occur. Certain long used and expensive medical treatments are being abandoned for lack of proof of effectiveness. Certain time-honored, costly and often mutilating surgical procedures are being seriously questioned as to their effectiveness. And even the effectiveness of some preventive measures such as the more or less sacred annual physical examination is under study. All this is as it should be and the effect should be to improve both the quality and cost of care. It should and will be continued.

However, a warning note should be sounded. Humans, whether sick or well, are not of one mold and each varies in some way from whatever norm is established. Humans make many decisions emotionally and these are often irrational rather than rational decisions. And not only are humans

highly individual and often highly irrational but faith plays an important role in their health care. This may be faith in a physician, faith in a system of health care or, in the case of a small child, faith in the teddy bear he takes with him to the hospital. As the effort to develop scientific proof of effectiveness in health care becomes more demanded and more documented, as indeed it must, the ultimate test of the effectiveness of any proof of effectiveness will be not only of how well it does away with unnecessary, ineffective and expensive procedures and services, but of how well its inherent and more or less systematized rationality adjusts to the inherent individuality and irrationality of those whose health and health care it is expected to serve.

Physicians can and should wholeheartedly support these trends to require proof of effectiveness in every aspect of health care. They are clearly compatible with medical science and are obviously in the best interests of patients and the public. No doubt some cows, long held sacred by the profession or the public or both, will be destroyed but this can only be for the good. There is little else in the offing which seems to hold as much promise of simultaneously improving the quality and reducing the costs in health care.

—MSMW

Learning Disorders

"Learning disorders" is becoming a household term. And why? It probably results from a series of circumstances, some real and some artifactual. During the last millisecond of civilization's time table some dramatic changes have taken place. The killers and cripplers—diphtheria, whooping cough, polio, measles, German measles and mumps—have become or are becoming medical rarities. We can state that undernutrition and deficiency diseases in the United States no longer affect large numbers of young children as long as we understand that our unfavorable infant mortality standing in the world, which is engendered by ill health in a select group of poor mothers, is still with us. Also, we have more money to spend on the chronically handicapped.

Yes, Dennis the Menace is receiving more attention, but what's new about him and his image? Very little, I suspect. What role do physicians have to play in the management of the problem? For one thing, they create new euphemisms to describe the problem, like the seven blind men feeling the elephant — "minimal brain dysfunction," "the hyperactive child," "the child with visual-motor imperception" or "brain damage," and "underachievers." This reminds me of McLuhan's "label-libel" gambit, a reference to the human tendency to dismiss an idea through the expedience of naming it. Yet who is in a better position than the physician to differentiate these youngsters diagnostically from their peers with the same set of behaviors? I am talking about the children who are emotionally disturbed, the "late bloomers," the nonscholars with superior manual skills and the gifted ones who are not challenged by the system. Maybe nobody is a better manager than the doctor, but let's face it, fellows: we don't really know much what we're talking about. The frequency with which one or the other etiologic diagnosis is made to explain the slow learning depends heavily upon the bias of the person whose opinion is sought, be he a generalist, a psychiatrist or a neurologist.

And what about some of the amazing treatment results we hear about? Now don't misunderstand, all good clinicians are daily forced to treat symptoms without a thousand dollar diagnostic workup and a full understanding of the symptom's cause. But is it at all surprising, if you "fix" a perverse and distractible child with a euphoriant drug which also sustains attention, that he will be more manageable and will increase his work output? Maybe the induction of a daily "high" in these children is the answer in some cases to maintain the mother's sanity, but how different is this psychologically and pharmacologically from some of the same agents self-administered to adults—in which case it is called "drug abuse"? I find the problem a knotty, circular one which bothers me because in some parts of the country this drug culture is being imposed upon increasing numbers of four-year-olds the way cod liver oil was fifty years ago.

I believe that Dr. Schain, whose review appears elsewhere in this journal, has done an exemplary job of describing where we stand *vis à vis* "learnin disorders," and I agree with his conclusions and his advice. We should assess our state of knowledge and avoid being guilty of the ignorance expressed in the aphorism, "He who knows not knows not that he knows not." Let's not be guilty of oversimplifying a very complicated problem

and let's not get too attached to our therapeutic triumphs which are largely anecdotal. Remember that our understanding of higher brain function is foggy at best. The best example of our rank ignorance in this field is to look at the scholastically brilliant overachievers at the other end of the educational spectrum. Among the latter group we must concede that we have no effective way of identifying in the long term the person who will be most effective and productive in his chosen field, regardless of whether you're selecting executives for IBM or candidates for medical school.

Concede that these children are clearly a mixed diagnostic bag, some with constitutional personality traits that lead to rebellion and maladjustment in the social artifact we call a classroom, some from broken and disturbed homes where food, shelter and clothing represent far more real challenges than mastery of reading, writing and arithmetic, some bright and gifted daydreamers whose only escape from the boring classroom humdrum is to buck the system by play-acting their dreams and fantasies and some whose deviant behavior results from actual neuronal damage. And to the physician whose primary responsibility is to identify disease, to treat it and to counsel parents when he identifies something untreatable, I would say in the current idiom, "Do your own thing." Manage every patient individually, try to make an accurate diagnosis and, when you get to the edge of your orbit, ask for help from other real specialists—the psychologists and educators.

Last, let's agree to study the problem carefully if it's that important and let's restrain our emotional attachments to a vague concept that in its essence is extremely complicated until we have something that resembles scientific evidence. If we decide to study the problem scientifically, let us plan the study in advance, define our terms, frame the questions carefully, agree to be patient while data are being collected and avoid trying to pool unpoolable data. More, let us invite the biometrists and geneticists to join the clinicians in planning the study and be especially careful about deriving conclusions about the effects of drugs on behavior especially if the observations are not controlled with the use of double-blind and placebo techniques that will lend credibility to the results.

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Acid-Base Changes During and Following Cardiac Resuscitation

DURING THE PAST DECADE, the importance of changes in acid-base balance occurring during resuscitation from cardiac arrest has been recognized with increased frequency. The report by Carrasco and Oletta[1] in this issue of CALIFORNIA MEDICINE emphasizes the severity of acid-base abnormalities detected during cardiac arrest, even when they occur in the most favorable situations for resuscitation—that is, in the operating room or in specialized diagnostic laboratories. This report also documents that serial follow-up measurements of pH, pO_2 and pCO_2 following resuscitation are essential for continuing care and for determining ultimate prognosis. Several practical and theoretical issues raised by these investigators merit further discussion.

First, the duration of cardiac arrest before it is recognized, and any delay in establishing adequate ventilation and circulation after recognition of arrest, have an important influence on the severity of the acidosis, and as indicated, on the ultimate survival of the patient. Metabolic and respiratory acidosis in combination appears to indicate a poorer prognosis, probably reflecting the fact that neither the circulation nor ventilation was restored adequately. Occasional over-correction of acidosis occurs during the initial resuscitation attempts, due to the administration of too much bicarbonate. Frequent measures of pH during resuscitation permits one to avoid this consequence. Furthermore, since many patients who experience cardiac arrest have underlying cardiac or pulmonary disorders which predispose to acid-base abnormalities, sequential measurement of pH, pO_2 and pCO_2 during a period of 24 to 48 hours after cardiac arrest seems essential. There are obvious complexities in managing those who are gravely ill and require assisted ventilation, gastric suction and intravenous feeding, and who have abnormal hepatic and renal function in their recovery from cardiac arrest. Clearly, those who remain unconscious due to central nervous system hypoxia, those who have inadequate restoration or permanent damage to the circulatory system and again develop metabolic acidosis because of inadequate oxygenation, those having major cardiac damage with pulmonary edema, and those who have long periods of arrest

before treatment, thus developing severe metabolic derangements, will have a poor prognosis for recovery.[1,2]

Second, in developing treatment programs for patients during cardiac resuscitation, emphasis should be given to several factors: (a) adequate ventilation, which frequently requires endotracheal intubation,[3] (b) the administration of bicarbonates based on frequent measurements of pH, since no formula for its administration can be established for every patient,[4] (c) the management of the entire medical and surgical problem of the patient by an experienced and practiced team in the hospital, and (d) the early recognition of the cardiac arrest. In many instances in an operating room or a special procedures diagnostic room, ventricular fibrillation can be recognized and terminated electrically before alterations in acid-base occur.

Third, patients who have cardiac arrest frequently have an abnormal acid-base status before the arrest,[5] due to underlying disease and/or prior drug therapy. Ultimate recovery depends not only upon excellent medical management, but upon the severity of the underlying disease.

Finally, correction of acid-base abnormalities in patients during and following cardiac arrest is important to restore the effectiveness of drugs such as catecholamines and antiarrhythmic agents, to prevent the recurrence of cardiac arrhythmias, which may be enhanced by the abnormalities, and to restore the function of vital organs such as the brain, heart, lungs and kidneys.

Clearly, the recognition of altered acid-base status and its correction during the resuscitation is of critical importance. Serial determinations to guide therapy for 24 to 48 hours afterward are required in many patients. The initial severity of the acidosis and its recurrence, considered together with the clinical status of the patient and his underlying disease, permit a prediction of the ultimate prognosis, as is stressed by Carrasco and Oletta.[1]

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Where We Stand on Drug Abuse

"WHERE WE STAND ON DRUG ABUSE," a statement which appears elsewhere in this issue, was prepared by the California Medical Association's Committee on Alcoholism and the Committee on Dangerous Drugs, endorsed by the Scientific Board and the Council, and accepted by the House of Delegates in March 1973. It is our understanding that this statement was more than a year in preparation and underwent several revisions. The document as finally approved represents one of the most carefully prepared and thoughtfully reviewed official statements on the subject by the medical profession to be found anywhere.

The statement is to be commended on two grounds. First and most important, it reflects the present state of the scientific knowledge concerning drug abuse and well-informed scientific and professional opinion as to how this knowledge might best be used at this time to deal with our admittedly serious drug abuse problem. This is its most significant contribution and the one which will have the most effect on patient care and the betterment of the public health. But the report also is one of the most carefully developed official statements ever adopted by the California Medical Association. It reflects not only the expertise of the Scientific Board, but the knowledge of experienced physicians who have had long and close contact with the problems of drug abuse, and finally the collective wisdom of the medical profession in California as expressed through its leaders on the Council and its representatives in the House of Delegates. Altogether the report is an example of an important statement by organized medicine and of how such a statement can be developed within the framework of this state association.

—MSMW

CASE REPORTS

Refer to: Hoffman RB, Zucker MO: A new technique in the treatment of renal bleeding: Epinephrine infusion in a patient with sickle cell trait. Calif Med 118:49-50, June 1973

A New Technique in the Treatment of Renal Bleeding

Epinephrine Infusion in a Patient with Sickle Cell Trait

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DURING THE LAST DECADE there has been an intense interest in pharmacologic agents in angiographic procedures.[1-9] Epinephrine has been used to enhance tumor visualization in the kidney[1-4] and gastrointestinal tract.[5] Vasopressors have been used to control gastrointestinal bleeding through infusions into the splanchnic arteries.[2,6-8] Renal artery epinephrine infusions have also been used to protect the kidney during radiation therapy.[3,9] A logical extension of the above work is the use of vasopressor infusion to control severe renal bleeding. Following is a report of a case in which we had opportunity to apply this technique.

Report of a Case

A 27-year-old Negro woman was admitted with severe gross hematuria and mild right flank pain. The patient had been a "sickle cell carrier" with intermittent microscopic hematuria of unknown etiology.

General physical examination was unremarkable except for mild right costovertebral angle tenderness. Admission urine was loaded with red blood cells and grossly bloody. Hemoglobin was 11 gm and the hematocrit was 33.2 percent. Hemoglobin electrophoresis revealed the hemoglobin to be of the SA type.

An intravenous pyelogram revealed mild caliectasis on the right with no evidence of obstruction. There was no radiographic evidence of papillary necrosis, and it was felt that the findings were compatible with chronic pyelonephritis. Cystoscopy revealed a jet of blood from the right kidney. Cultures from the right ureter revealed 1 plus growth of E. coli and cultures from the left kidney were negative.

Following cystoscopy, 5 ml of 10 percent silver nitrate solution were instilled into the right renal pelvis. Bleeding diminished for an hour but then resumed. One unit of whole blood was given. Hematuria continued and the following day the hemoglobin content was 9.8 grams and the hematocrit was 30.1 percent. Another unit of whole blood was given. Bleeding persisted and right nephrectomy was considered, but it was decided first to attempt an epinephrine infusion into the right renal artery in hope of controlling the hematuria.

A catheter was percutaneously passed into the right renal artery, and a selective arteriogram revealed extravasation of contrast medium from an upper pole artery and a "pruned" appearance of the distal vessels in the right upper pole (Figure 1). It was not clear whether these changes were from multiple end artery infarcts or from chronic inflammatory disease. Epinephrine was infused into the right renal artery at the rate of 10 μg per minute for ten minutes.

Following the procedure there was a pronounced decrease in hematuria, and by the following morning the urine was clear. The patient left the hospital and was seen at weekly intervals with no recurrence of gross hematuria. Although microscopic hematuria has been noted intermittently, the hemoglobin content and the hematocrit have remained stable.

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Submitted July 10, 1972.

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Figure 1.—Selective right renal arteriogram revealing extravasation of contrast from upper pole artery (arrow). Note "pruned" appearance of upper pole vasculature.

Discussion

This was the first known attempt to apply the principle of arterial vasoconstriction to renal bleeding. In this case, extravasation of contrast from the bleeding vessel was identified. In instances where this is possible, a post-infusion arteriogram could graphically demonstrate whether the infusion was successful, but, as Rosche et al have pointed out, the vasodilatory effect of contrast may exacerbate the bleeding and necessitate a repeat infusion.[8] Monitoring of bleeding is more direct in the urinary tract than in the gastrointestinal tract due to the indwelling catheter.

The dose of epinephrine used was 10 μg per minute for ten minutes which is slightly greater than that used to protect the kidney during radiation therapy. A mechanical pump such as the Harvard pump is preferred for the infusion. Our patient experienced a dull ache in the flank during the infusion, a phenomenon that has been reported by Steckel et al with their infusions in preparation for irradiation of the renal bed.[9]

Although the cause of the bleeding in this case was never firmly established, immediate therapy was deemed necessary due to the heavy loss of blood. Obviously, the infusion could not be used to control bleeding from vascular neoplasms or arteriovenous malformations since the vessels would not show normal vasconstriction when stimulated by epinephrine.

The following categories of renal bleeders may be ideal candidates for infusion:

- Patients with massive hematuria who refuse operation for any reason.
- The renal bleeder who has only one kidney or such severe bilateral disease that nephrectomy could not be tolerated.
- The post-traumatic renal bleeder who has multiple systems traumatized and preferably could have nephrectomy deferred or made unnecessary.

Summary

A patient with sickle cell trait and uncontrolled hematuria with the source localized to one kidney was infused for ten minutes with 10 μg per minute of an epinephrine solution directly into the involved renal artery. There was prompt cessation of the renal bleeding. This technique appears promising, particularly in selected cases of gross hematuria when operation is contraindicated.

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Refer to: Friedmann CTH, Spiegel EL, Aaron E, et al: Leptospirosis ballum contracted from pet mice. Calif Med 118:51-52, June 1973

Leptospirosis Ballum Contracted from Pet Mice

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A PATIENT was recently treated in a hospital in Los Angeles County, California, for an illness clinically resembling leptospirosis. Laboratory tests were diagnostic for the serotype Leptospira ballum. Epidemiologic investigation revealed the source to be the patient's two pet white mice.

Report of a Case

A 37-year-old Caucasian man, a parole officer, was admitted August 12 1971 to the Kaiser Foundation Hospital, Panorama City, California, with a history of headache, fever, myalgia, vomiting and diarrhea of three days' duration. On admission, the body temperature was 39.8°C (103.6°F) but there were no other positive physical findings. Pertinent admission laboratory data included leukocytes numbering 5,000 per cu mm of blood, with 69 percent segmented neutrophils and 11 percent banded neutrophils, and hemoglobin of 12.5 grams per 100 ml. Three days later leukocytes numbered 4,200 with 88 percent segmented neutrophils. Serum glutamic oxalic transaminase was 90 Sigma-Franklin units, total serum bilirubin was 0.9 mg per 100 ml, and alkaline phosphatase was 36 international units. Three days later serum alkaline phosphatase was 72 international units, SGOT 72 Sigma-Franklin units, and serum bilirubin 0.6 per 100 ml. Urinalysis and blood cultures were negative for pathogenic organisms.

During the first 24 hours after admission, a morbilliform rash developed over the patient's chest, and because of the possibility of rickettsial disease he was treated with tetracycline, 500 mg orally four times a day for 14 days. Twelve hours after this treatment was begun, fever began to diminish and on the third day in hospital it abated completely. The rash cleared on the fifth day and the patient was discharged two days later.

On September 8 1971 the patient's temperature rose suddenly to 37.8°C (100°F) and headache, myalgia, and bilateral testicular tenderness developed. The testicles were enlarged and tender on physical examination. The leukocyte count was 9,700 per cu mm and hemoglobin was 14.7 grams per 100 ml. Results of urinalysis and urine and blood cultures were negative. Ampicillin, 500 mg four times a day, was given for ten days, and on the third day of treatment the symptoms disappeared.

Specimens of serum drawn during the acute and the convalescent phases were sent to the Center for Disease Control at Atlanta to be tested for antibodies to leptospirosis by the agglutinin-absorption method.[1] The specimen drawn August 13 at the acute stage was negative. The specimen drawn August 18 was positive for L. ballum at a dilution of 1:800, and that of September 7 was positive at a dilution of 1:25,600. This constituted a titer rise consistent with the diagnosis of leptospirosis, serotype ballum.

Epidemiologic Investigation

The patient lives with his wife and three daughters, aged 9, 11 and 13 years, none of whom has had a similar illness. He denied any known contact with dogs, rats, or other animals while on duty as a parole officer. He had no history of swimming or of outdoor camping or hunting before the onset of illness. About two months before he became ill he had had contact with a sick dog at the home of his parents in Denver. A serum specimen obtained from the dog by the Colorado State Department of Health in mid-September 1971 was negative for all types of leptospira antigens. The patient's own household had a pet cat, a parakeet and two pet white mice. The mice, which had been purchased at a local pet shop May 13 1971, were clinically well and housed in a cage. All members of the family took part in cleaning the cage and handling the mice. The mice were killed on September 14 1971, and examined at the County of Los Angeles Veterinarian's Office. Histopathologic examination of sections stained by hematoxylin and eosin revealed nephritis in both. Warthin's silver impregnation stain of renal sections revealed many leptospires. Organisms from fresh kidney tissue were cultured on Vervood's medium and then inoculated into

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three guinea pigs. Serum specimens taken from the guinea pigs before inoculation and two weeks later were examined for antibodies to ballum and five other serotypes. A titer rise from negative to 1:48 against ballum was found in two of the three animals; the titer against the other five serotypes remained negative.

The pet shop owner stated that during May he had purchased mice from four persons who raised small litters for sale. Two of the four suppliers could not be traced. Two mice obtained from one of the available suppliers were killed and examined. They had normal kidneys free of leptospires on histopathologic examination. A brown mouse obtained from the other supplier had leptospires in the renal tubular epithelium. A serum specimen taken from that mouse was positive for antibodies to ballum at a dilution of 1:196. Serum obtained from the man and woman who owned this mouse were tested and showed no titer for leptospira antibodies.

On September 18 and October 2 1971 serum samples were obtained from the four members of the patient's family. All were negative for leptospira antibodies. The patient, when asked why he rather than other members of his family might have become ill, speculated that one of his daughters, after an argument, had used his toothbrush to clean the mouse-cage. The patient did not become aware of this until September. His daughter could not recall the exact date the toothbrush had been used in this way, but the best estimate appeared to be between the middle and the end of July.

Discussion

The patient experienced a biphasic disease which was compatible with the textbook description of leptospirosis.[2] At first he had fever, rash, myalgia and gastroenteritis, which disappeared by the sixth day of illness. A month after the onset, he had a second phase consisting of fever, orchitis, headache and myalgia that lasted three days. Symptoms subsided each time shortly after the initiation of antibiotic therapy. This may have been coincidental, as the efficacy of antibiotic treatment initiated later than the second day of illness has not been proved.[2] The elevated SGOT and serum alkaline phosphatase are also compatible with the diagnosis.

Between 1947 and 1970, only 16 cases of ballum infection in humans were recorded in the United States.[3-6] Eight of these occurred at one laboratory.[5] Detailed clinical descriptions of only five of the 16 cases are available in the literature.[5,6] In all five the patients had orchitis, a symptom not generally associated with leptospirosis. Orchitis occurred during the initial phase of the disease in one patient, while the other four had it during the second phase. All five contracted their illness through contact with laboratory mice. The patient in the present case is the first known to have become infected from contact with pet mice. Rats and mice are the common animal hosts for ballum, although the infection has been found in opossums, skunks, rabbits, foxes and wildcats.[7] The infection in mice and rats is inapparent and often persists for life.[8] Several colonies of laboratory mice have been found to harbor the organism.[5,8] However, no estimate is available as to the general carrier rate among laboratory and pet rodents within the United States. As the disease in humans is often difficult to diagnose, the incidence among owners of such animals and among laboratory workers may be much higher than is suspected.

Summary

A patient was recently treated in a hospital in Los Angeles County, California, for an illness clinically resembling leptospirosis. Laboratory tests were diagnostic for the serotype Leptospira ballum. Epidemiologic investigation revealed the source to be the patient's two pet white mice. This case is only the sixth of L. ballum in humans described in detail in the United States literature. The five others were contracted through contact with laboratory mice. Since the diagnosis of leptospirosis in humans is often difficult to make, it is possible that the risk to laboratory workers and owners of pet mice might be greater than is currently thought. No estimates are available as to the carrier rate among laboratory rodents in the United States.

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Refer to: Williams RR, Schweitzer RJ: Clear-cell adenocarcinoma of the vagina in a girl whose mother had taken diethylstilbestrol. Calif Med 118:53-55, June 1973

Clear-Cell Adenocarcinoma of the Vagina in a Girl Whose Mother Had Taken Diethylstilbestrol

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THE REPORT BY HERBST AND SCULLY[1] in 1970 of a cluster of seven cases of adenocarcinoma of the vagina in adolescents is of singular importance. Six of the cancers were of clear-cell type while the seventh was endometrioid. These lesions were diagnosed and treated in the interval of 1966 through 1969. In a later retrospective investigation, using matched controls for eight patients, Herbst et al[2] identified a statistically significant relationship between the maternal use of diethylstilbestrol or related congeners and the occurrence later of postmenarchial vaginal cancer in their daughters.

Greenwald et al[3] further reported five cases of primary vaginal adenocarcinoma occurring in postmenarchial adolescents under the age of 20 years. These cases were collected from the New York State Cancer Registry and occurred in the period 1950 through 1970. In all cases the mothers of these patients had received synthetic estrogens during early pregnancy.

These observations document lucid examples of transplacental carcinogenesis induced by maternal administration of synthetic nonsteroidal estrogen compounds.

The following case is illustrative of the delayed association of administration of synthetic nonsteroidal estrogen to mothers in early pregnancy with the postmenarchial onset of vaginal adenocarcinoma in their offspring.

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Report of a Case

The patient, aged 18, was first examined in October 1970 because of irregular vaginal bleeding. On self-examination she had discovered a thickening at about mid-vagina. Biopsy of the posterior vaginal wall was interpreted microscopically as adenocarcinoma, probably mesonephric in origin.

When the patient was admitted to hospital November 22 1970, the vaginal bleeding had ceased. The past history was unremarkable. Menarche had occurred at age 13 with regular periods usually of six days' duration. There had been no previous abnormal vaginal bleeding. Neither hormones nor oral contraceptives had been administered.

The patient's father as well as three brothers and one sister were living and well. Her mother had died of unknown cause. It was verified that the patient's mother gave a history of early miscarriage. During the first four months of the pregnancy which resulted in delivery of the patient at term, the mother had been given diethylstilbestrol orally, 25 mg four times daily.

Pelvic examination revealed circumferential thickening and induration of the posterior vaginal wall. The abnormal area was situated about 3 cm above the introitus and extended to the lateral aspects. On visualization, the area was nodular to granular and discolored by irregular hemorrhages. The lesion extended circumferentially over the posterior mid-vaginal surface from about 3 o'clock to 10 o'clock. There were small granulating areas on the portio anteriorly near the os and within the anterolateral fornices. Pelvic and rectal findings were otherwise normal. Extensive studies, including serum chemical determinations, peripheral blood cell counts, urinalysis, a chest roentgenogram, a skeletal survey, an intravenous pyelogram and cystoscopic as well as proctoscopic examination, were all essentially normal.

On November 24, following confirmation of the original biopsy diagnosis, a Wertheim hysterectomy with right salpingo-oophorectomy, vaginectomy, resection of the anterior rectal segment and including pelvic lymphadenectomy, was performed. The left oviduct and ovary were preserved. Sigmoid colostomy, appendectomy and vaginal reconstruction were also carried out.

The main pathological specimens consisted of the uterus, right oviduct and ovary, the vagina and a segment of posterior introital skin as well as



Figure 1.—Excised vagina, showing circumferential thickening, nodularity and hemorrhages due to the tumor.

separately received pelvic lymph node dissections. Significant findings were limited to the vaginal surface (Figure 1). The posterior vaginal wall approximately 4 cm above the introitus was thickened, indurated and nodular. There were patchy superficial vaginal mucosal hemorrhages. Moderate circumferential erosion of the cervical portio was present near the external os. The uterus, right oviduct and ovary as well as the pelvic lymph nodes and appendix were grossly normal.

Microscopical examination of the vaginal tumor revealed clear-cell adenocarcinoma confined to the vaginal wall (Stage I). The lesion appeared superficial in origin, deeply infiltrative and irregularly ulcerated at the surface. The epithelial configurations were solid, tubular, ductular, often cystic and frequently papillary (Figure 2). The individual tumor cells were quite large, with pleomorphic often gigantic and frequently multiple nuclei. Nucleoli were conspicuous and occasional mitoses were observed. The cytoplasm was variably clear to dense. Periodic acid Schiff stains confirmed abundant cytoplasmic and lumenal glycogenic material. Adenosis was present and manifest by multiple benign glands scattered widely beneath the mucosal lining at the margins of the adenocarcinoma. These resembled normal glands of both cervical and endometrial type (Figure 3). The adenosis as well as the clear-cell adenocarcinoma were considered to be of mullerian origin. There were no infiltrations of lymphatic spaces by the tumor, and sections of all of the pelvic lymph nodes were free of metastasis. The sections from the cervix showed pronounced epithelial erosion with chronic granulation tissue formation extending into the portio, and were otherwise benign.

The patient progressed normally and was discharged December 1, the sixteenth postoperative day. After subsequent convalescence she was readmitted January 28 1971 for sigmoid colostomy closure with end-to-end anastomosis. She has remained well.

Discussion

In the original report including six cases of clear-cell adenocarcinoma of the vagina, Herbst and Scully[1] indicated that in one patient, 16 years of age, the lesion was inoperable and she died five months after biopsy. One additional patient was apparently cured by local excision. The remaining four patients were treated by Wertheim resections with vaginectomy and pelvic lymphadenectomy and were considered cured.

In Greenwald's[3] series of five cases, three

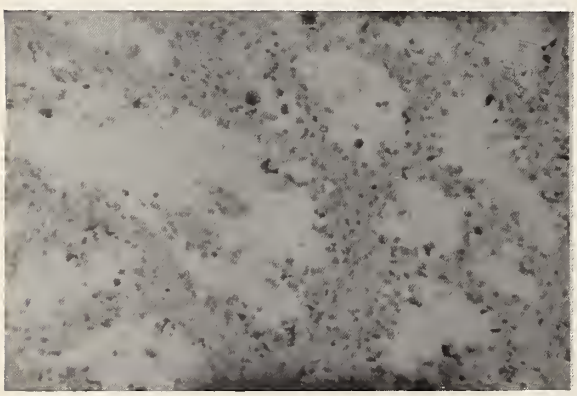


Figure 2.—Malignant glands lined by clear cells with occasional hobnail cells (× 100).

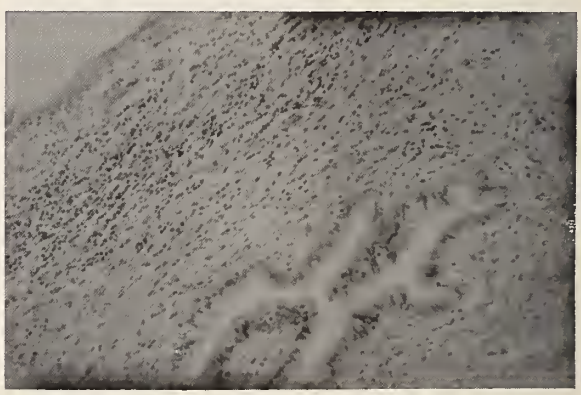


Figure 3.—Adenosis with ectopic benign endocervical type gland within vagina (× 100).

patients died in advanced stages of the disease. Diagnosis had been made within two months of the onset of symptoms in all three. The fourth patient had symptoms for 18 months before treatment by anterior exenteration, vaginectomy and pelvic lymphadenectomy. The fifth patient had had symptoms for five months before radical hysterectomy and vaginectomy were carried out. The ovaries were left intact and she was considered cured.

In a recent report of 91 registry cases of clear-cell adenocarcinoma of the female genital tract, Herbst et al[4] included 53 cases primarily of vaginal origin. Survival data according to staging were available in 43 cases. All of 28 patients in Stage I survived. Three of 12 with Stage II were dead, and all three with Stage III disease died. The overall series of vaginal adenocarcinomas showed 13.7 percent mortality. By comparison, six of twenty-two patients with primary clear-cell adenocarcinoma of the cervix have died (27.3 percent mortality). Follow-up periods were less than two years in a number of cases in both series.

The foregoing data all reflect the high morbidity and mortality in patients with clear-cell adenocarcinoma as well as the necessity for early detection and radical surgical treatment. There are reasonable indications that the ovaries can be safely spared and that vaginal reconstruction will restore sexual function.

Herbst[4,5] quite conservatively has withheld the conclusion that administration of diethylstilbestrol and congeners during early pregnancy of the mothers of these patients is the sole etiologic factor. The duration and concentration of dosage in relationship to embryologic development of the vagina in the first trimester appear as the prime circumstances predisposing to later onset of clear-cell cancer. Other hormonal and environmental influences may be causally related. It must be noted in eight of the 69 cases in Herbst's[5] series in which maternal histories could be elicited there were no records of stilbestrol therapy. Earlier, Plaut and Dreyfuss[6] as well as Hertig and Gore[7] documented the relationship of adenosis as a precursor stage to the development of adenocarcinoma within the vagina. Hertig and Gore in particular related adenosis and vaginal adenocarcinoma to embryonic vestiges of mullerian structures. Neither Plaut and Dreyfuss nor Hertig and Gore attributed these findings to administration of nonsteroidal estrogen compounds.

Because of widespread administration of diethylstilbestrol and congeners in treating high risk pregnant patients in the 1940's and 1950's, hundreds of thousands of young female patients are now theoretically at risk. Very likely, vaginal and cervical adenocarcinoma will be seen to occur with increasing frequency as this select group remains under the continuous stimulus of ovarian produced estrogens. It will be of critical interest to further evaluate the effects of increasing age, administration of estrogens, other hormones, hormonal contraceptives and pregnancies upon the incidence of malignant disease in this group even though risk factors may seem to be low for individuals.

Meanwhile, we are obliged to view abnormal vaginal bleeding and related symptoms in postmenarchial patients with greater concern and to perform careful cervical and vaginal examinations in these cases. We should attempt further to identify patients who are at risk by appropriate review of the obstetrical histories of the mothers concerned.

It appears that the use of stilbestrol as a postcoital contraceptive may no longer be prudent in view of its possible role in carcinogenesis.

Summary

In the present case, vaginal adenocarcinoma occurred in a young woman years after her mother had taken diethylstilbestrol during pregnancy. As there are many hundreds of thousands of young women currently at risk, we are obliged to watch for and promptly investigate irregular bleeding and other vaginal symptoms in this group. Attempts should be made to trace the offspring of mothers who received diethylstilbestrol during pregnancy in order that regular vaginal examinations may be made.

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LETTERS *to the Editor*

Annual Session

To the Editor: The 102nd Annual Session of the CMA was as usual a great success. There may be, however, some areas where your gentle readers may wish to voice their concern for improvement. I refer to the Scientific Section Meetings. Many of these were excellent. There were also a number of worthwhile social conferences on topics such as Data Processing, Marriage, Medical Writing, Alcoholism and so forth.

There might have been much more. The choice of meetings and the availability of conferences devoted to a variety of special subjects seemed to be wanting. Perhaps there are others who feel as I do. The excellence of California medicine should be reflected in the annual meetings of our association.

We started a scientific association. Now that the specialty organizations have assumed this responsibility, CMA has developed increasingly socio-economic interests for the betterment of the profession. Possibly the pendulum has swung too far. Now as a common meeting ground for the specialty societies, may not the CMA again assume leadership as a scientific society as well as its proven leadership in socio-economics?

Much has been done already to coordinate meetings of the specialty societies with the annual sessions. Further development of this policy could very easily transform these sessions to a rewarding educational experience for CMA members. Quite possibly an even better attendance might result.

Philip L. Pillsbury, MD
San Francisco

More on Gonorrhea

To the Editor: Dr. Nelson's review of uncomplicated male gonorrhea [Calif Med 118:10-13, Jan 1973] was undoubtedly accepted for publication months ago. It needs some updating now. But first may I object to our sloppy Public Health publicity that talks about venereal disease being *the* major communicable disease, as if "it" were *one* infection. What organism is responsible and what are the specific symptoms of *the* venereal disease? The statistics are impressive enough without lumping together gonorrhea, infectious syphilis, and all the latent reactive serologies uncovered each year—a meaningless melange. We might as well talk about the incidence of dysentery and include shigellosis, salmonellosis and viral gastroenteritis as one disease—shades of the nineteenth century.

In listing sites of entry of the gonococcus, the pharynx should be included among less frequent portals of entry, along with the conjunctivas and rectum.

Although Dr. Nelson does mention asymptomatic gonorrhea in the male, I believe he would agree that it now deserves more than passing mention. Every female, who has gonorrhea and is not named as a contact to a male case, should be interviewed and her recent contacts at least examined for asymptomatic infection. A significant proportion will be found to be infected.

At present oral treatment of gonorrhea is most easily accomplished (unless the patient is penicillin sensitive) with 3.5 grams ampicillin and 1 gram probenecid given at the same time in one dose in the clinic (a lot of pills but surprisingly well tolerated). This dosage is not adequate to protect certainly against incubating syphilis, but there are some advantages in avoiding intramuscular penicillin and in not having to keep patients waiting 30 minutes after the oral probenecid before giving the injectable medication. Our clinic has utilized this dosage of ampicillin and probenecid for the last 18 months with no evidence of increasing resistance and a treatment failure rate of less than 7 percent.

Mary Riggs, MD
San Jose

Chiropractic and Exposure to Radiation

To the Editor: In an editorial in JAMA (May 15, 1972), it was urged that, in the same manner as for cigarettes, chiropractors' offices be posted as follows:

> Warning: The Department of Health, Education and Welfare Has Determined That the Chiropractic Method (Unscientific Cultism) Is Dangerous to Your Health.

To support this contention, for which the tongue may have been abducted if not actually touching the cheek, there was reference to an HEW study of chiropractic practice which concluded:

> Chiropractic theory and practice are not based upon the body of knowledge related to health, disease and health care that has been widely accepted by the scientific community. Moreover, irrespective of its theory, the scope and quality of chiropractic education do not prepare the practitioner to make an adequate diagnosis and provide appropriate treatment.

Although the danger of chiropractic practice to health may not have been quantitated in its entirety, the Department of Public Health of the State of California has now made available information on the extent of x-ray exposures delivered to patients by chiropractors in California.[1] Extrapolating from a 20 percent sample, it was found that the 1,308 chiropractors with registered x-ray equipment do 5,840 examinations of the lumbar spine each week. Of these, 1,749 are 14 x 36 inch films of the entire spine. The examinations average two exposures each. Assuming a dose of a rad per exposure, this one procedure alone would account for in the order of half a million man-rads per year, an exposure approximately 1,000-fold greater than to the entire U.S. population from all currently operating nuclear power plants.

More importantly, the evidence seems abundant that the technical quality of these films is often so poor that interpretation is impossible. In reviewing chiropractic films of members insured by the National Association of Letter Carriers, Dr. Wallace Cole, a radiologist of the Washington Clinic, found over 50 percent of some 300 sets of film totally unfit for any diagnostic purpose. He found only one subluxation. In another case, 20 sets of films submitted with a chiropractic diagnosis of subluxation were reviewed by a team of radiologists who were unable to diagnose a single subluxation. Subsequently, the National Association of Letter Carriers deleted their insurance coverage of chiropractic coverage.

The issues seem clear: good public health practice cries out for elimination of this abuse of diagnostic radiation. Not only are there risks to the exposed population alone, but the collective gene pool itself is at some hazard. No matter how small, the absence of any diagnostic advantage to chiropractic radiology requires action to abolish this public menace.

Leonard A. Sagan, MD
Palo Alto

REFERENCE

1. Kinsman S (Director, Radiologic Health, California State Health Department): Personal communication

Refer to: Where we stand on drug abuse—Statement by the California Medical Association Committee on Alcoholism and the Committee on Dangerous Drugs. Calif Med 118: 58-64, June 1973



Where We Stand on
Drug Abuse

FOREWORD . . .

IMPROPER USE OF ANY DRUG IS A HEALTH AND MEDICAL PROBLEM FIRST

When a person shows medical indications of physical or psychological dependence on any drug, that person should receive competent medical care. All physicians, all hospitals and all health insurance carriers should assume their respective responsibilities for medical management of the alcoholic and drug dependent patient. Therefore, we urge physicians to seek training and practical experience in the techniques of diagnosis and treatment associated with drug abuse problems including alcoholism. We urge the establishment of training programs in medical schools, in community hospitals and at postgraduate levels with extension of training to nurses and paramedical personnel.

We urge that physicians fully understand the legal rights and status of the patients, as well as their own legal responsibility in treating patients who are drug users. Where laws, local ordinances, rulings or procedures interfere with providing necessary care or violate patient-physician confidentiality, all resources of the medical profession and the public should be directed toward eliminating this interference.

Flexibility of attitudes on all sides of the issues, positive changes in laws and changes in some existing enforcement procedures will be required to meet the problems created by the improper use of drugs.

NOTE: The sections of this report which reiterate basic factual information are shown in standard type. *The sections which represent a position, or which tell where we stand, are shown in italics.*

THE DRUGS OF ABUSE are defined as those drugs which produce mood alteration or mind alteration —those drugs which are psychoactive.

The term drug abuse will be understood to mean the use of any drug by an individual to the extent that it adversely affects or limits his ability to function as a responsible person.

Methods of categorizing or ranking the drugs of abuse depend upon the purpose and the criteria of the classifier. We recognize that all such rankings are somewhat arbitrary, and that many variable factors such as different age and socio-economic groups, different geographical locations and the percentage of the population involved could alter the order of such a list.

For example, when drugs are placed in a rank order primarily on the basis of physical organ damage, current information would suggest that they be listed in this order, beginning with the most damaging:

1. alcohol
2. tobacco
3. amphetamines
4. solvents
5. barbiturates
6. heroin and other narcotics (in their pharmacologically pure form)
7. cocaine
8. hallucinogens
9. hashish
10. marijuana
11. caffeine

This statement was prepared by the California Medical Association Committee on Alcoholism and the Committee on Dangerous Drugs, endorsed by the Scientific Board and the Council, and accepted by the House of Delegates, March 10-14, 1973.

Reprint requests to: California Medical Association, Attention: Gail B. Jara, 693 Sutter Street, San Francisco, Ca. 94102.

For this paper, however, it seems more appropriate to rank the drugs of abuse in the approximate order of their physical damage, psychological and socio-economic disruption taken together. The order then is:

1. alcohol
2. barbiturates
3. amphetamines
4. heroin and other narcotics (in their adulterated, contaminated form available for street use)
5. cocaine
6. hallucinogens
7. marijuana and hashish
8. solvents
9. tobacco

Alcohol

Alcohol in all its forms is a drug of the sedative hypnotic class[1] which is fully available (in fact, advertised) and whose social use is widespread. The extent of use and the effects vary from person to person.

Acute short-term alcohol intoxication, chronic use short of alcoholism and alcoholism itself each represents a serious form of drug abuse. When evaluated in terms of organ damage, the effect on the user's overall health, societal disruption, association with criminal behavior or total population involved, alcohol abuse is the most serious form of drug abuse in our society today—*even more serious than heroin addiction.*

The California Medical Association's Committee on Alcoholism has defined alcoholism as a chronic disabling disease of unknown cause, characterized by physiological, psychological or socio-economic disturbances in a person that impair his ability to function in a normal, acceptable manner within his environment.

Diagnosis of alcoholism should not be based on the amount of alcohol ingested, but rather on the disruptive effect of whatever amount is taken. The diagnosis of alcoholism is difficult to document; however, these major and minor symptoms have been defined.

Major symptoms of alcoholism:

1. in some persons, the occurrence of severe withdrawal syndrome; that is, the appearance, within a few hours of the last drink, of symptoms (such as, severe tremulousness, alcoholic hallucinations, withdrawal seizures or convulsions, delirium tremens)[2] which interfere with the ability of the person to function or to meet the responsibilities of the moment;

2. in some persons, the fact that they do not appear to be intoxicated despite very high blood levels of alcohol;

3. continued drinking despite strong medical reasons not to, or social reasons such as the loss of a job or spouse.

Minor symptoms of alcoholism:

1. results of certain laboratory tests demonstrating liver damage or other chemical derangements;

2. surreptitious drinking;

3. frequent automobile accidents or traffic violations;

4. drinking to relieve anger, insomnia or depression;

5. repeated attempts to "go on the wagon," with failure.

Generally speaking, a diagnosis of alcoholism is strongly indicated when any one of the major symptoms is present, or any combination of two or more of the minor symptoms. Such findings should lead to further diagnostic probing in order to establish the diagnosis of alcoholism.

The treatment of alcoholism falls into at least three phases. The patient is detoxified or treated for the acute state of intoxication (first phase). In the chronic alcoholic, this detoxification may be followed by relatively severe withdrawal symptoms which must then be treated (second phase). Long term treatment (third phase) is usually designed to achieve the abstention from all alcoholic beverages. The physician should be prepared to give pharmacological as well as psychological support as needed during these phases of treatment.

The California Medical Association recognizes the use of alcohol as one of the most destructive forms of drug abuse in our society today. CMA does not advocate prohibition of alcoholic beverages. It does advocate intensive public education, in all grade levels and through the mass media, concerning the harmful effects of alcohol. Since there are widespread advertisements promoting the use of alcohol in its various forms, the mass media should be careful not to present alcohol in such a fashion as to promote its use as a mood-altering drug.

1. Alcohol compounds the effects of other sedative hypnotic drugs such as barbiturates and may have more serious effects when taken in such combinations.

2. Severe withdrawal symptoms need not occur after every drinking episode.

Alcoholism must be recognized and treated as a disease which has become a public health concern of major proportions—challenging heart disease, stroke and cancer as the Number One health problem of the country. The application of specific criteria for the diagnosis of alcoholism should help correct a current imbalance, namely, over-diagnosis among members of the lower socio-economic groups and under-diagnosis in the middle and upper income groups.

CMA recommends that insurance coverage should no longer exclude the treatment of alcoholism or place restrictions on the coverage provided, except as they may apply to any other medical illness.

Barbiturates, Other Sedative Hypnotics and "Minor" Tranquilizers

Examples of barbiturates, other sedative hypnotics and "minor" tranquilizers are:[3]

secobarbital, Seconal®, "reds;"
pentobarbital, Nembutal®, "nembies, yellows, yellow jackets;"
amobarbital, Amytal®, "blues, blue heavens;"
combination amobarbital and secobarbital, Tuinal®, "rainbows;"
phenobarbital, Luminal®, "phennies;"
methaqualone, Quaalude®, Sopor®, "sopors;"
meprobamate, Miltown®, Equinil®, "mother's little helpers;"
diazepam, Valium®, "vals;"
chlordiazepoxide, Librium®, "libs."

This whole group of drugs is collectively known as barbs, downers, goofers, sleepers, and other such terms.

Barbiturates are central nervous system depressants used for treatment of insomnia and relief of anxiety. Continued use produces tolerance and physiological addiction as well as psychological dependence on the effects of the drugs. Doses higher than the individual's tolerance produce a state of deep anesthesia which is followed by respiratory and circulatory depression.[4] Overdose can be fatal.

A problem as grave as acute intoxication and overdose is chronic barbiturate use, which resembles one of the major symptoms of chronic alcoholism—that is, signs of intoxication are not present even when large amounts of barbiturates are present in the body.

Withdrawal from heavy barbiturate use can present a major medical emergency for which hospitalization is often required because of convulsions (sometimes resulting in compression fractures of the spine and possibly death), lack of oxygen or accumulation of abnormally large amounts of fluid in the lungs or brain may result in death. Extensive care after withdrawal is usually required to establish personal stability and to replace the psychological dependence.

The "minor" tranquilizers are drugs ordinarily prescribed to relieve anxiety. Continued use in larger than usual doses produces a dependency.

Physicians should be aware of the abuse potential (addiction potential) before they place a patient on any of these drugs.

Amphetamines

Examples of drugs classified as amphetamines are:

amphetamine, Benzedrine®, "bennies, cross tops, whites;"
methamphetamine, Methedrine®, Desoxyn®, "meth, crystal, speed, beans;"
dextroamphetamine, Dexadrine®, "dexies;"
dl-amphetamine resin, Biphetamine®, "black beauties;"
combination of dextroamphetamine and amobarbital, Dexamyl®, "Christmas trees."

This whole group of drugs is collectively known as uppers, speed, pep pills, et cetera.

Amphetamines are central nervous system stimulants used in the treatment of certain hyperactive neurologically impaired children and in the treatment of narcolepsy. They have also been used to suppress the appetite, elevate the mood and ward off fatigue. Such use sometimes leads to abuse patterns.

People who continually take larger amounts because of increasing tolerance experience extreme psychological dependence and may suffer mild physical withdrawal symptoms when deprived of the drug.

Heavy use of illicitly manufactured or distributed amphetamines (particularly intravenous use) produces some of the more extreme examples of abnormal behavior and erratic mind alteration. Self-destruction, criminal and psychotic behavior are so commonly associated with abuse of stimulants that we feel positive legislative and public health measures are justified in order to control their traffic.

Their use for military and athletic purposes should be thoroughly investigated and submitted to critical analysis.

The continued use of amphetamines for pur-

3. For each classification of drug, several examples are cited by generic term, trade name and street name, in that order. These lists are meant only as representative examples and cannot be considered exhaustive because street names change continuously and new drugs come into use. Furthermore, street names vary in different areas of the state.

4. In combination with any other central nervous system depressant, such as alcohol, the effects are intensified.

poses other than treatment of properly diagnosed narcolepsy or hyperkinesis in children should have clear medical justification. This policy is an essential step toward reducing the excessive manufacture and distribution of these drugs.

Narcotics or Opiates

Examples of narcotics or opiates are:

diacetylmorphine, heroin, "junk, smack, horse, cheeva;"
morphine, "morf, white stuff, Miss Emma;"
methadone, Dolophine®, "dollies, dolls, J-72's, biscuits;"
hydromorphone, Dilaudid®;
meperidine, Demerol®;
oxycodone, Percodan®, "percs, endos;"
methylmorphine, codeine, "fours, schoolboy;"
opium alkaloids, opium, "O, black stuff, hop;"
camphorated tincture of opium, paregoric;
hydrocodone, Hycodan®.

Narcotics are drugs which are prescribed for the relief of pain and also for sedation and sleep. Continued use of heroin or other narcotics produces increasing tolerance, addiction and a strong psychological dependence on the effects of the drug. In the addict with high tolerance, the use of heroin does not necessarily produce either a "rush" or euphoria, but rather is required to maintain normal functioning and to stave off the symptoms of withdrawal.

The narcotics themselves, in their pharmacologically pure form, produce little or no organ damage. The injurious effects to the individual and society are due not to the chronic action of the drugs on the body, but to the hazards which accompany their illegality and the addict's life style—for example, risk of poisoning by adulterants mixed with the drug by the supplier (dealer), risk of blood borne infections (such as hepatitis) from use of dirty or shared needles, risk of overdose from unknown or varying strengths of the drugs, and often the addict's poor hygiene and health habits.

Irrespective of how it develops, once addiction is established, it is a disease which requires medical services and social rehabilitation. The medical aspects of the disease (including medical records, which must be held confidential) must be separated from the criminal aspects of the behavior and legal status of the individual patient, so that treatment may be readily available to every addict who seeks it.

In- and out-patient detoxification to treat withdrawal symptoms (both with and without narcotics such as methadone), half-way houses or living groups which provide surrogate families and peer pressure, and methadone maintenance should all be available in sufficient numbers. They have all been successful to some degree in the treatment of patients addicted to heroin.

In a properly structured methadone maintenance program, the administered methadone itself is only a part of the more complete and complex therapeutic and rehabilitative regime. Adequate attention must be given to these resocialization activities in order to establish personal stability and to replace the psychological dependence on the drug. The ultimate aim of the use of methadone as a treatment tool—as is the aim of the other treatment modalities mentioned above—is to enable the patient to lead a stable, drug-free life.

The fact that addiction to methadone is produced during the period of maintenance and the potential diversion of methadone to street use are both recognized as disadvantages of these programs. Nevertheless, for many addicts such treatment programs become a practical, though not ideal, alternative to the criminalization phase of their addiction.

A uniformly successful treatment modality is not presently available; therefore, we encourage responsible investigation toward this end, and we oppose any governmental regulation or professional rigidity which would promote or require any single modality at the expense of others—whether proven or experimental.

Cocaine

Cocaine is also known by such names as snow, "C", coke, flake, Bernice, nose candy, rich man's drug, snuff and snow bird.

Cocaine is an ancient drug—a stimulant distilled from the coca plant. It is used medically as a topical anesthetic. At present we are witnessing an increase in the illicit use of cocaine for central nervous system stimulation. The effect is similar to that of amphetamines. Cocaine does not require a constantly increasing dose to achieve the desired effect, and discontinuance does not lead to a withdrawal syndrome. Repeated application of cocaine to the nasal membrane for rapid absorption may lead to destruction of the nasal septum.

Strong warnings should be issued that continued usage leads to deterioration of health because of nervous fatigue, nutritional deficiency and psychosocial defects. Psychological dependence is the rule in the habitual user.

Hallucinogens or Psychedelics

Examples of hallucinogens or psychedelics are:

lysergic acid diethylamide, LSD, "acid, sugar, cubes;"
phencyclidine, PCP, "angel's dust, hog, peace pill, elephant"—often misrepresented as THC;
trimethoxyphenethylamine, mescaline, "mesc, big chief, cactus, peyote;"
psilocybin, "mushroom, silly putty;"
STP (DOM), "serenity-tranquility-peace pill;"
DMT, "businessman's special;"
tetrahydrocannabinol, THC.

Hallucinogens are chemicals, or drugs, whose name indicates that they produce hallucinations, or more often, illusions. Continued use does not produce physiological addiction, but does often result in psychological dependence on the effects of the drugs. Little physical damage to organs is attributed to the pharmacological action. Nevertheless, damage to health and the results of aberrant behavior while the user is under the influence of the chemical are very real dangers.

There should be intense scientific investigation to discover the long range effects of hallucinogens, their potential social uses, their value as tools in clinical medical practice and their value in the investigation of the physiology of the central nervous system. However, unsupervised and indiscriminate use of these drugs should be vigorously discouraged.

Marijuana and Hashish

Marijuana, or cannabis sativa, is also known as pot, hay, grass, bush, dope, weed, tea, et cetera. Marijuana cigarettes are known as joints; the small end of such a cigarette left after most of it has been smoked is called a roach.

Hashish is a more potent agent made from the resin of the marijuana plant.

Marijuana is a psychoactive agent whose principal known ingredient, tetrahydrocannabinol (THC), produces sedative and hypnotic effects which can alter a person's mood and behavior to varying degrees—depending on such factors as dose and the setting in which it is taken. It is not a narcotic.

The full range of marijuana's action is currently undergoing intensive scientific investigation. The major consistently observable physical effects in low doses of marijuana use are reddening of the eyes and increase in heart rate. The smoke is irritating to the mucous membranes it reaches. In low doses, its principal actions involving brain functions are subjective; they are described variably as illusion, sensory changes and short-term memory loss.

Long-term effects are not yet known. However, our experience with the long-term effects of drugs such as alcohol, barbiturates and tobacco leads us to anticipate the possibility of physical or psychic damage, unless prolonged years of observation and evaluation exclude such damage.

The California Medical Association encourages research and clinical trials to determine the effects of marijuana's action. CMA feels that, if such research shows marijuana or its active ingredients to have therapeutic properties useful for medical purposes, these substances should be made available for such purposes.

As with other drugs, the exact classification of marijuana in the laws regulating controlled substances should be based on accurate pharmacological definition and accepted research data. Marijuana is not a narcotic. It is hoped that those responsible for legislation will respond to the definition of marijuana as it was stated by the National Commission on Marijuana and Drug Abuse.

The act of legalizing marijuana is one which society must ultimately decide. We do feel that it is the role of the medical profession to provide the scientific facts and interpretations on which such a decision can be based.

On the other hand, the question of reduction of penalties in cases of marijuana use might well be reviewed in light of its medical implications as a primary health issue. The current penalties for the possession of marijuana for personal use, even in private, have imposed criminal status on many persons who otherwise have evidenced no criminal or anti-social behavior. The effects of imprisonment on one's mental and physical health and the effect of a felony conviction on one's future career and emotional stability are among the several health factors to be considered when judging the merits of decriminalization of marijuana. Consequently, the California Medical Association recommends the appropriate reduction of penalties for possession of marijuana for personal use.[5]

There is a certain paradox in advocating decriminalization because of the difficulty of identifying the place at which the possession or transfer of marijuana becomes a criminal act.

5. We refer the reader also to the position of the American Medical Association's House of Delegates (1972) and to the position of the AMA's Committee on Alcoholism and Drug Dependence (1972).

However, the health issue inherent in imprisonment and conviction is an important one, and one on which CMA can take a medical position. As a logical extension of that medical position, comes our advocacy of reduction of penalties.

Solvents and Other Inhalants

Inhaling the fumes of solvents (volatile hydrocarbons such as airplane glue and paint thinner) produces effects ranging from mild intoxication, to acute disorientation, to death. Continued use is responsible for toxic effects upon the brain, kidneys, liver and bone marrow.

Repeated use should call attention to the psycho-social problems of the user, and those problems should be treated medically. The dangers of experimentation must be countered by education.

Tobacco

Tobacco is only minimally psychoactive, is fully available (in fact, advertised) and is not generally considered a drug of abuse. However, most people are now aware of the direct correlation between cigarette smoking and lung cancer. Even more significant, in numbers of people killed and disabled, are cardiovascular disease, bronchitis, and other chronic pulmonary disease caused by cigarettes. Cigarette smoking not only contributes to but may be the direct cause of many of these problems.

While supporting each person's right to freedom of choice, the California Medical Association condemns the use of tobacco as one of the most physically destructive forms of drug abuse in our society today. We recognize that the rights of the non-smoker to breathe air free of cigarette smoke should be given appropriate consideration.

Since much of the damage produced by smoking is potentially reversible, we encourage individuals to give up the smoking habit, and we applaud the efforts to develop treatment modalities aimed at curing tobacco habituation.

We advocate intensive public education in all grade levels and through the mass media concerning the harmful effects of smoking.

Prescription Drugs

Almost all the examples listed under the sections on barbiturates, narcotics and amphetamines are prescription drugs that can be abused either licitly, by prescription, or illicitly by using an altered prescription or obtaining the drug from the black market or the street.

Any drug that is capable of inducing changes in mood or altered states of consciousness is potentially a drug of abuse. The abuse of legally manufactured drugs intended for medical treatment has become a serious problem in recent years.

We strongly recommend that drug manufacturers, drug wholesalers and pharmacists, who are responsible for large quantities of dangerous drugs or drugs with abuse potential, make the utmost effort to insure that these drugs are directed only to legitimate therapeutic uses. The physician should use great care regarding the size of the drug prescription and his refill procedures in order to avoid possibilities for abuse. The public should guard against the use of a prescription drug by anyone other than the person for whom it was prescribed, thus preventing opportunities for abuse and protecting children from possible poisoning.

We encourage signed letters of complaint to the local county medical society and to the Board of Medical Examiners[6] documenting specific instances of misuse of drug prescription practices by a patient or physician.

Over-the-Counter Drugs

Some drugs available over-the-counter are used for psychoactive effects and are thus subject to abuse patterns; for example, cough syrups containing either detromethorphan or low doses of codeine, such as Robitussin-DM® or Romilar® and sedatives such as Nervine®, Compoz®, Sleep-Eze®, Nyquil®.

The public has a right to purchase and self-administer certain drugs that have a wide margin of safety without resorting to medical advice. However, such drugs dispensed over the counter (O.T.C.) without prescription are frequently misused. Drugs for pain relief, asthmatic attacks, hemorrhoids, itching, hyperacidity, constipation, etc. are advertised and dispensed O.T.C. and often self-administered as a substitute for proper medical care of the primary cause of these ailments.

California Medical Association wishes to direct attention to the advertising policies of some of the manufacturers of these drugs. The effects of psychoactive drugs, such as those which maintain wakefulness or induce sleep, are exaggerated. The basic ingredients of most psychoactive drugs on

6. Board of Medical Examiners, 1020 "N" Street, Room 434, Sacramento, California 95814.

the market tend to vary little, but advertising claims imply great advantages of one over the other.

It may be the right of drug manufacturers to so advertise; however, the right to use federally licensed media to disseminate unsubstantiated or exaggerated claims should be prohibited, or such advertising should be closely monitored for accuracy.

The repetitive recommendations in the advertising of O.T.C. drugs tend to reinforce the drug orientation of this society, as well as to reinforce the human urge to overcome internal conflicts and external pressures by taking a pill.

Multiple Drug Use

Many persons use several drugs together, in abuse patterns. A common example is the use of "downers" such as barbiturates or heroin by those who use large amounts of amphetamines or cocaine. The downers are used to counteract the undesirable prolonged effects of the stimulants. Another pattern is the combination of alcohol with barbiturates, which may be additive in their effects. This is an especially dangerous combination because the two sedative hypnotics intensify the effects of one another in a synergistic relationship and can easily result in severe physiological changes such as respiratory depression, coma or possible death from overdose.

We endorse vigorous education efforts to advise the public of the compound dangers which result from this drug taking practice.

Conclusion

Drug abuse—with the many factors contributing to it—is not a single issue but a collection of many complex, inter-related psychological, physical and social problems not isolated from the other problems of our communities; such as, employment, housing, education, police relations. Since many aspects of these problems are unique in each locality, local action and involvement are necessary to confront them.

California Medical Association recommends the establishment of sound, comprehensive treatment programs in which the whole community actively contributes to the social readjustment of the patient.

Sources of pamphlets and other informational materials are:

American Medical Association, 535 North Dearbon Street, Chicago, Illinois 60610

American School Health Association, P.O. Box 416, Kent, Ohio 44240

American Social Health Association, 785 Market, San Francisco, California 94103, or 1740 Broadway, New York, New York 10019

California Blue Shield: Pamphlet: *Drug Abuse: The Chemical Cop Out*, 1969, 720 California Street, San Francisco, California 94108

DARE (Drug Abuse Research and Education), UCLA Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, California 90024

Haight-Ashbury Publications, P.O. Box 27278, San Francisco, California 94127

National Clearinghouse for Drug Abuse Information, P.O. Box 1701, Washington, D.C. 20013

National Clearinghouse on Smoking and Health, Health Services and Mental Health Administration, 5600 Fishers Lane, Rockville, Maryland 20852

National Institute on Alcohol Abuse and Alcoholism, 5600 Fishers Lane, Room 6C 15, Rockville, Maryland 20852

The following is a short listing of references given here only to indicate some sources of further information. These references will provide additional bibliographies.

First Special Report to the U.S. Congress on Alcohol and Health from the Secretary of Health, Education and Welfare, December, 1971. Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, price $1.50, stock number 1724-0193

Marijuana: A Signal of Misunderstanding—First Report of the National Commission on Marijuana and Drug Abuse, March, 1972. Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, $1.00 (paper cover), stock number 5266-0001

Appendix to Marijuana: A Signal of Misunderstanding, Volumes I and II—The Technical Papers of the First Report of the National Commission on Marijuana and Drug Abuse. Superintendent of Documents, address above, $10.75 per 2 volume set (paper cover), sold in sets only, stock number 5266-0002

Drug Use in America: Problem in Perspective—Second Report of the National Commission on Marijuana and Drug Abuse, March, 1973. Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, $2.60, stock number 5266-0003

Appendix to Drug Use in America: Problem in Perspective. Superintendent of Documents, address above, available in early summer of 1973

The Use and Misuse of Drugs, Stanley Einstein. Wadsworth Publishing Company, Inc., Belmont, California, 1970

Drug Abuse Information Project, Annual Reports to the Legislature, 1967-1971. Drug Abuse Information Project, University of California, San Francisco, San Francisco 94122

Love Needs Care, David E. Smith, M.D. and John Luce. Little, Brown and Company, Boston, 1971

"It's So Good, Don't Even Try It Once"—Heroin in Perspective, David E. Smith, M.D., George R. Gay, M.D., Editors. Prentice Hall, Inc., Inglewood Cliffs, New Jersey, 1972

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Special Article

Management and Marketing in Health Care

Some Lessons for the United States from the British System

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The British health care system has been examined by sociologists, political scientists, and medical care specialists before, but in this presentation a section of the British health care system is viewed through the eyes of modern business management, particularly as to cost and consumer effectiveness. Examination of positive features as well as problems may be helpful in relation to some future health care delivery system in the United States. Cross fertilization between the disciplines of management and medicine has much to offer to the rapidly changing delivery of health care in the United States.

PREFACE: This article is an interdisciplinary effort. Robert Gumbiner, MD, executive director of Family Health Program, visited the British Isles to study the ambulatory care system. His orientation is that of the chief executive of an existing prepayment group practice (HMO) and includes over 15 years of experience in the management of ambulatory care facilities. He combines academic input as Adjunct Professor and director of the program in Management of Health Care Delivery Systems at California State University at Long Beach. Dr. Gumbiner's observations were then combined with those of Robert Frye, Doctor of Business Administration and Professor of Management, California State University at Long Beach, in order to bring to bear on the problems facing the ambulatory care system in Scotland and Ireland an additional orientation and expertise.

A review of the history and current status of the British system reveals that, in many respects, it has advanced beyond the United States system, both in theory and practice. In fact, some facets of the British experience could well serve as a guide for the evolution of our health care delivery system.

THE SCOPE OF THIS REPORT is limited to the ambulatory care section of the British health care system, principally in Scotland and Northern Ireland. This represents a deliberate attempt to obtain insight into these smaller, more flexible units which appear to represent some of the most advanced elements of change.

It appears that the British system is confronted by a number of philosophical obstacles to the evolution of an optimally effective health care system. However, a reorientation of thinking to managerial and marketing basics would go a long way toward overcoming these obstacles.

There are lessons in all this for legislators, planners, and providers as they attempt to design a

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system for the United States. These lessons are particularly pertinent because of the context in which the British and United States systems have developed. The British forthrightly did something that the United States, with its massive resources, has failed to do. In 1948, with less medical manpower and money per capita than the United States, Britain simply legislated a new health care delivery system and made it work—at least within the constraints that were imposed by uncontrollable conditions. On the other hand, the legislative and executive branches in the United States have been complaining about our ineffective system for years—yet have done little more than nibble around the edge of the problem with stop-gap measures that can, at best, only shore up a failing system piecemeal.

History and Current Status of the British System

In reviewing the British system, it was deemed most appropriate to study the elements where the bulk of medical care should be administered—the ambulatory care center. In addition, by concentrating on two smaller, self-contained geographic and administrative units of the system—the Scottish Home and Health Service and the Irish Ministry of Health and Social Services—a more comprehensive view of relatively progressive elements was achieved. It appears that there is an inverse relationship between the size of the self-governing unit and its progressiveness.

History of the system. In 1912, the British enacted the National Health Insurance Act. In reality, this was a national health insurance program with somewhat limited care. While it covered most outpatient ambulatory care services, it allowed for very few hospital services. Similarly, while it covered a wide variety of services under a variety of coverage plans, it usually provided only for the employee and not his family. Nor did it provide for the self-employed or the unemployed.

This 1912 legislation gave way, in 1948, to the present National Health Service—an attempt to provide a more comprehensive level of care to the British. Even more important, it was an attempt to deliver this health care to all Britons, whenever and wherever they needed it.

Finally, in 1968, the first British green paper was published. This highly significant advance was a review of the British health system and its progress since 1948. Many of the recent developments in the system can be traced to the remedial measures contained in this paper.

Current status of the system. The British health system is divided into three spheres of authority. One administers the hospital service, including specialists, who are all hospital-based. It also sets pay scales for the specialist sector of the doctor population.

A second section administers local health services and is somewhat akin to our Public Health Service. The Local Health Authority controls health officers, health visitors, and various public health functions such as sanitation, food, well-baby care, and prenatal care.

The final sphere of authority administers ambulatory care, with control over the general practitioner and his services. Further, it administers the capitation and service payments and, as we shall see later, the development of ambulatory care centers.

The Executive Council is an integral part of this general practice section. It is somewhat like our comprehensive health planning councils, but possesses vastly greater powers. Authorized under National Health Service, it is composed of lay citizens and doctors. The Executive Council is charged with the responsibility for, and limited to authority over, general practitioners in its geographic area. It handles complaints and inquiries, and—in a very unstructured manner—attempts to exercise some control over the quality and accessibility of care.

Geographic balance. The most important function of an Executive Council is, in a sense, to license general practitioners to practice in its area. Without Executive Council authorization, an applicant general practitioner can practice in an area only if he chooses to do so outside the National Health Service system. This means that he can receive no payment through the system.

The Executive Council approach represents the British attempt to come to grips with a universal problem in the delivery of health care—the elimination of imbalance between areas that have too many doctors and those with too few. Approval will not be given for new practices in areas that are adequately served. However, in an area where there are too few the doctor will begin with a ready-made panel of patients, or at least with his name listed in the local postoffice as available for assignment of patients.

One of the side benefits of this system is the ease with which the consumer can locate a general practitioner. A visit to the postoffice produces a

list of all available practitioners in the area who have room on their panels.

This mandatory distribution of doctors, as well as consumer accessibility to primary care doctors, represents an impressive advantage over the United States system.

Balance between specialists and general practitioners. The universal problem of imbalance between the services of the general practitioner and the specialist has been attacked directly through application of the great equalizer, money. The general practitioner is provided with an immediate income greater than the average for specialists. Typically, as soon as he gets his medical degree, the general practitioner earns some 4,000 to 5,000 pounds a year. The specialist, on the other hand, must serve a period as a "registrar" in a district hospital. This includes his residency training and beyond, averaging about 15 years—a period during which he starts at about 2,000 pounds a year and reaches a maximum of 3,500 pounds a year several years later. As a registrar, the doctor must wait until a position opens as a "consultant" in order to increase his income. Since the system is not expanding rapidly, his appointment must await the death or retirement of the consultant he is to replace.

The typical general practitioner not only will realize a greater immediate income, over his lifetime he will probably earn more money than a specialist. The specialist still retains greater prestige and presumably, for him, more interesting work.

By this simple device of reversing the usual monetary reward system, the British have gone far in decreasing the trend toward over-specialization and the disappearance of the generalist as we know it in the United States.

Optimum utilization of facilities and management. Perhaps the outstanding feature of the British system, particularly in Northern Ireland and Scotland, is the sincere attempt to bring health care to the consumer by establishing local health centers for the combined use of general practitioners and Local Health Authority personnel. This trend brings together two important elements of ambulatory care into a single facility.

Amalgamation is taking place at a higher organizational level as well, with an effort being undertaken to merge the three sections of the system—hospital, Local Health Authority and ambulatory care—into a more cohesive unit. Ideally, this combined administration would assign tasks to each sphere of influence in accord with its capabilities and assure the most effective utilization of resources in order to eliminate the empire-building inherent in any such tripartite system.

Sporadic attempts have been made in the United States to combine ambulatory neighborhood treatment centers, health departments and county hospitals. We could do well to observe how the British are approaching this on a national scale.

The Ambulatory Care Center

Ambulatory care centers in Scotland range all the way from brand new centers, constructed specifically for ambulatory care and community health services, to a remodeled civil defense building in the inner city of Edinburgh or the ambulatory care section of a district hospital.

Typically, ambulatory care units house seven or eight doctors. However, this is not truly a group practice. Rather, it is a series of small partnerships of two or three doctors who "cover" for one another. The several partnerships simply share the same facilities, and have little in common other than centralized record-keeping, receptionists, and minimal ancillary services.

Although the ambulatory care center is a recent development in the British system, it is highly developed in Northern Ireland where, it is expected, all general practitioners soon will be working from these centers. It is in Ireland that the local health services sector has made the most progress in constructing ambulatory care centers which include quarters for general practitioners, health visitors, the district nurse, the well-baby and prenatal clinic, the nutritional center and some social services.

The contrast between care delivered in a center of this sort and typical health care delivery in the United States is unsettling. In this country, a mother may go to the public health department for well-baby care. Then, if the baby is sick, she may have to travel across town and find a physician to treat the child. In the Irish system, the mother would simply walk across the hall to get treatment for her baby. In these centers, there is valuable interaction among the professionals; for example, doctors can send a health visitor to evaluate a patient in his home, and experts in nutrition and social service counselling are available on the premises.

Several major problem areas exist in the portions of the present British system we examined. Although these same problems exist in the United

States, we were surprised that they still exist in a system that has been operating since 1948. Innovators, as the British have been, of course may be expected to make mistakes; but it is hoped that as the United States develops its health care system, these same errors can be avoided.

Intersectional conflict. The arbitrary tripartite nature of the total system in Britain reduces its effectiveness. Duplication exists in services provided by the general practitioner and also by the local health authority and the hospital section. Problems in coordination and follow-through can be severe, and the competition for funding from the National Health Service among hospital specialists, community health services, and general practitioners creates administrative burdens.

In addition, there appears to be a power struggle between the local health-general practitioner and the hospital-specialist sections of the system. On the one hand, the hospital-specialist section is attempting to capture ambulatory care for the district hospitals. One such attempt involves luring general practitioners into the hospitals and making "ambulatory care specialists" out of them.

On the other hand, the local health-general practitioner section is attempting to integrate specialists, particularly of the primary care type such as pediatricians and internists, and assign them to the ambulatory care centers to provide ongoing consulting services.

A pilot project in Edinburgh is of interest. A simplified x-ray machine is available to some general practitioners who have been trained to use it. However, the hospital-specialist section maintains enough control to keep those same general practitioners from reading even the simplest of the x-ray films that they take.

Administrative personnel should take an objective look at all the different problems and all the different sectors of the delivery of medical care, then make optimal allocation of resources without constantly considering whose domain might be infringed upon, whose power interfered with, whose toes stepped on.

Productivity

The general practitioner's day appears to be rather relaxed. Typically, it was found that the day begins at about 9 o'clock. The period from about 9 to 11 in the morning is spent in consulting with patients in the center. Even here, examinations may not be thorough—one doctor said that he deals with ten patients an hour.

After the morning stint of two hours the doctor spends an hour or so chatting with colleagues, bringing his paperwork up to date (not a great task since the administrative staff seems to be comfortably large—the only one that is), and drinking coffee. Following this, he usually leaves about noon to make home visits until 4 p.m. (There is some evidence that home visits are not overly taxing—the Briton is beginning to accept the idea of visiting the center for treatment rather than having the doctor "drop by.") Finally, the doctor will round off his day with an hour or two from 4 to 5 or 6 p.m. spent back in his office seeing patients.

Despite large panels in some areas, it is unlikely that a physician's panel will contain many more than 2,000 patients. Many general practitioners, in fact, have panels with as few as 1,200—small when one realizes that the general practitioner provides only a portion of each patient's care, other portions being provided by the hospital specialist and the local health authority. This leads an observer to question the productivity of the typical ambulatory care physician.

This points up the unfortunate problem of the lack of control exercised over either the quantity or the quality of medical care that is delivered. The system is spending money without demanding performance from the physician measured against standards. A physician can get away with a three-hour work day and, further, can see either six patients during that time or sixty patients, with no control over either quality or quantity.

This serious question about general practitioners' productivity in the British system goes far beyond a relaxed attitude toward working hours. First, there appears to be minimal utilization of ancillary and paramedical personnel, or even effective use of those few who are present.

Second, the physician's productivity is severely hampered by the lack of laboratory and other aids—basically he is able to do only what he can do with his hands.

At least in concept, the greatest cost in any health care system is the cost of personnel. This does not seem to have had much impact on the British health system administration. Simple installations—x-ray units and laboratories—in ambulatory care centers would save enormous amounts of time for the total system—doctors, ancillary people and consumers. Instead, the British general practitioner can do little more than examine a patient and, if he feels it is necessary, bundle him

off to a district hospital to specialists or for x-ray examination or laboratory tests.

The ponderous course of interaction between consumer, general practitioner and specialist shows clearly the lack of regard for productivity. Despite the inconvenience of traveling, a patient in need of specialists' services, or even simple laboratory tests, is sent off to a district hospital where he may have to wait for hours. Then he returns to his general practitioner, who may have to wait days for a report.

Or the consumer's convenience may be served at the expense of physicians' time: A general practioner asks for consultation, a specialist travels out from the district hospital, and both may visit the patient in his home. This procedure almost invariably takes an entire afternoon of two physicians' time.

A narrow view of cost containment precludes the general practitioner's achieving real productivity. Denying him basic facilities, such as x-ray and laboratory, saves capital expenditures at that center but results in greater total cost through manhours lost. A non-objective element here may be a matter of innate jealousy on the part of specialists who do not want general practitioners to impinge upon their domains.

This inability to understand the principle of making optimal use of all of the elements in a system has adverse effects on the physician himself. Not only is the ambulatory care physician's time not adequately utilized, but his skills also. It seems wasteful that a physician who has training in orthopedics, minor surgery and internal medicine should spend all his working day simply screening minor complaints and shuffling them off to hospital-based specialists.

Facilities

Whether it is a collection of general practitioners' offices, a combined public health-general practitioner center, or the ambulatory care section of a district hospital, the British ambulatory care center is likely to be poorly designed from a functional point of view even when it is aesthetically pleasing. Although many are new, neat and clean, much space may be devoted to nonfunctional areas such as halls and staff rooms. It appears that the centers have been designed by persons outside of the health care delivery system and without substantial input from the people working in the centers.

In many instances this is obviously true—first the centers were built, then the doctors were lured into them by some rather innovative techniques. One of these techniques calls for the health center physicians to pay rent for their quarters and wages for the ancillary health worker. Then, this money is returned to them in the form of additional incentive pay for using the centers.

An example of a minor sort of problem that complicates fundamental, substantive problems is the relatively crude system of appointments and record-keeping. First, even the concept of patient appointments is a new one in the British system and is handled differently than in the United States. The physician stacks on his desk the records of patients who have appointments, and calls them in one by one from the top down. This obviously allows no provision for late cancellations and walk-in patients, even emergency cases, and provides no system for screening patients by relative need. The records themselves are typically about the size of 3 x 5 file cards, and entries are seldom over one line in length—evidence of deficiencies in quality control and systems management.

The British ambulatory care system appears curiously ambivalent toward ancillary staffing in its ambulatory care facilities. On the one hand, physicians practicing in centers are relieved of substantially all of their paper work and enjoy the services of ample reception staffs. On the other hand, the lack of nursing attendants is startling. Typically, a center will have one or two nursing personnel who administer shots and dressings, but are seldom utilized in assisting a doctor in examination or treatment.

Usually there are no medical group or health center managers. In a few instances a nurse or ancillary with a "few weeks' training" in management was being used—a real lack of sophistication in management method.

Consumer Orientation

Great progress could be made through the proper utilization of services, and proper application of both physicians' and consumers' time.

Consumer orientation for all providers including doctors would probably overcome the present inefficiencies with regard to the use of health center x-ray and laboratory facilities and change the system under which specialists are available only in large district hospitals far removed from the patients they are to serve. Certainly consumer orientation would be a force against centralizing

portions of the ambulatory care system in these major regional hospital centers.

One might argue that the British physician's willingness to make home visits is an example of consumer orientation. By the same token, one might argue that credit and home delivery extended by the corner grocery store would be a sign of consumer orientation. In either instance, the result is a high-cost, less-than-effective operation which can do nothing but raise costs to the consumer, cut down on the quality and availability of products or services, and fail in its mission to provide what it is supposed to provide in an optimum system.

Philosophical Obstacles

There are three major philosophical obstacles to improvement in the British health care system. These are (1) bureaucracy, (2) adherence to tradition, and (3) a lack of consideration of the system in its entirety.

Bureaucracy. As might be expected of a system that has been evolving for two generations, and in a society keenly aware of protocol, there is a substantial bureaucratic structure within the system.

As has been pointed out, the various sections of the bureaucracy have not yet come together with common goals. Although the ambulatory care and the local health sections seem to have gotten themselves together—using the combined health center as a vehicle—the hospital-specialist section seems to be completely unaware of the total concept of providing care to the consumer in the best possible manner.

However, the reverence accorded large hospitals is not confined to the hospital-specialist section. On the contrary, the local health-ambulatory care section management clings to the idea that huge district hospitals are the most effective means of delivering care.

As is typical in a bureaucracy, the concept of consumerism is lost. The bureaucrat tends to lose sight of the consumer as a person, and to perceive him as only a problem to be dealt with.

Administrative caution may well be the underlying reason why neither cost nor quality is controlled. To an outsider, the reason for want of control may seem humorous: One administrator, replying to a question, said that he keeps a "firm grip on costs" by refusing many of the requests for new equipment submitted by junior residents—a short-sighted view of cost control.

Of greater importance of course is quality control. There is no reason to believe that medical doctors cannot be good, bad and indifferent. All medical care providers should work under a control system to upgrade the quality and quantity of their work, a system which is constantly moving and constantly adapting to conditions, in order to get the maximum amount of quality productivity for the minimum amount of cost. In the British system, as in the United States system, protectionism of the doctor is rampant.

Adherence to tradition. Despite all his good intentions, the British administrator or physician finds it difficult to break away from the way things have always been done. Hence efforts to build a modern system are faced with problems that are inherited from the old days.

Perhaps one of the most obvious examples is the general acceptance of the need for the "home visit." It was interesting to note that the responses to the question, "Why so many home visits?" were not directed to the philosophical question but rather to the mechanics. It was pointed out that fevered children have always been visited at home, that old people are cared for in their homes, and so on. The answer literally is, "That's the way we've always done it."

In many instances, it was recognized by physicians that bringing patients into medical centers makes a lot more sense than going out to see them in their homes. However, it was suggested that many home visits were made because of a fear that someone will report the doctor if he does not make house calls.

These problems of segmentation of the system and the lack of quality and quantity control all exist in the United States. It is disappointing that the British in a more controlled system have not yet conquered them.

Needed: Managerial Orientation

In several areas there seems to be something less than a complete understanding of management principles. Only in Northern Ireland has there been an attempt to integrate the planning function with the organizing and control functions necessary to implement plans.

Elsewhere, there are planning groups that are stoutly resisting any such integration. This arrangement very neatly permits the planning group to abdicate its responsibilities for making a program work, and the administrative group to blame poor planning.

Another needed management input is at the level of the ambulatory care center. There is little recognition of the role that can be played by professional management here. However, when professionalism does make itself evident, there is a great demand. In one instance, for example, a health center engages in the practice of training a health service nurse as an administrator. The problem is that, as soon as one becomes trained and effective, higher authority steals her away.

Systems thinking. A systems approach toward health care delivery would preclude the British orientation toward massive hospital facilities. In general, large hospitals are more efficient than small ones in delivering hospital care; but the areas served by them are also large, which leads to "dehumanization" and, hence to ineffective service to the people in their service areas. The end result of course is a less effective total system. Even among people who express a favorable attitude toward the concept of localized health care delivery, there seems to be a bias against small hospitals. The emphasis is on maximizing the single element of a system—the hospital—rather than the the system as a whole. It appeared from our observations, however, that having more small hospitals and more services in the ambulatory care centers would save time for both the consumer and the provider and raise the general level of health care for the system as a whole.

This is not to suggest that systems planning is a panacea. Rather, it is a systematic inquiry into objectives, goals, standards and resources, and the most effective combination of these resources into a total system.

General Management and Marketing

Management thinking in the British system needs to be oriented toward cost control, particularly with regard to production control. Doctors under the system are paid according to the number of patients on their panel. This is, in itself, good, but there is no outside control exercised over either the quantity or the quality of their practice.

Better management could lead to better use of equipment and office space. Although doctors use their facilities only a portion of each day, there is no attempt to share. Rather, each doctor has his own examination room-office; and in addition a good deal of space is given to hallways, staff lounges and the like.

The British system of health care delivery needs a marketing strategy. First, an effort should be made to identify the needs of the market—that is, the consumers. Do the consumers want or will they use the services provided? Are the services appropriate for that market? One cannot but wonder whether this system was developed by the provider and then prescribed like a medication to the consumer. An effort to involve the consumer in the design of the system is not apparent.

Another marketing function, health education, including public relations or advertising, appears not to have been extensively used in a system which should make maximal use of it. In this context, we are not thinking of health education in the traditional disease-oriented sense but in relation to making both the consumer and the provider aware of the best way to make the best use of the system.

Proper marketing would be a major contribution to a cost-effective system and at the same time raise the level of health of the population. As it is, it is difficult to believe that the British system—working the way it does—could actually care for the total population if that population were utilizing as it should the primary care and health maintenance services. It might well be that the system is only serving those who recognize their illness, know about the available care, and can reach it.

The lack of management conceptualization and application is obvious. First, there is no integration between planning and doing—a basic principle of management. Second, there is very little attention paid to the cost-effective organization of personnel, facilities, and equipment. Third, the concept of systems management is lacking. Finally, no apparent attempt has been made to apply modern marketing techniques to the system.

Summary of the Pros and Cons

The British system through the establishment of certain controls has made better distribution of medical care, both geographically and by specialty, than has been accomplished in the United States. The British have come a long way toward solving the problems of "undoctored" areas and the problems of needless overspecialization that still exists in the United States. The average person has more ready access to physicians and, most important, the economic barrier between the doctor and patient has been removed. Care is fully paid for and physicians can be readily located. Both the doctor and the patient feel that they are better off under the British program as it operates today than they

were before the program was begun, in 1948. In general, the doctor has more to work with, has the support of his colleagues, and enjoys a more financially stable and professionally rewarding career. The consumer has readier access to health care without the fear of economic disaster as the result of sickness.

The whole British program represents a radical thrust on the part of the government to effect a change without the half-hearted, half-way measures we are experiencing and are liable to experience in the future.

On the adverse side, there are important problems which could be remedied. The system is slow, cumbersome, bureaucratic and tradition-bound. There is little input of modern management techniques, particularly in the integration of planning with actual operations and the application of general management and systems techniques. Although the system is dominated by the doctor providers, those basic providers have had little to do with the design of facilities or their use. While bowing to the preconceived and poorly tested traditional idea of the role of the doctor in control of health care delivery, those who manage the system have at the same time not allowed the doctor to join in implementing improvements in his effectiveness. Continuing the doctor in the traditional dual role of both manager and production worker can only deprive the system of quality and quantity control.

The very basic business of finding out what the market wants in a product or service before designing or providing it, has been ignored. Nothing is being done to sell the objectives and goals of the system to the consumer and to the provider. The total concept of cost effectiveness is poorly understood. Instead of design of the system as a whole for long-range cost effectiveness, there are short-range, piecemeal efforts that can only lead in the end to a more costly system. Although the British system has gone much further in developing a logical health care delivery program than the United States, it does not yet have a cost-effective total system responsive to all elements, including providers, consumers, and government.

Lessons for the United States

The British put their system together without due regard for management principles. Here in the United States, where we possess managerial skills in abundance, there can be no excuse for repeating British mistakes—we should apply our skills initially and continually.

Whatever our system, it should not replay the British tune. Rather, it should establish and work toward a common set of goals. Planning should be integrated with system operations. Control should be exercised to see that goals are achieved. The effectiveness of the total system should not be sacrificed to achieve a maximum effectiveness for one element in it.

A serious British error is their lack of control over quantity and quality of output. We have traditionally made this mistake, depending on some sort of cost control through price resistance in the marketplace or through insurance carriers' manipulation of benefits—controls that have obviously failed. In the United States we may do well to regard the British demonstration as an object lesson in the need for managerial control.

Marketing research techniques should be applied, first, to generate inputs as to need from both providers and consumers of medical care and, second, through aggressive marketing communication techniques to persuade both providers and consumers to utilize their system in the most productive manner possible.

The British have achieved a far superior geographic balance of medical care delivery than we have, as well as a better balance between the services of the general practitioner and the specialist. We should examine carefully their systems of monetary incentives and licensing to determine whether some features can be adapted to our context. Another British accomplishment, the amalgamation of community health services and ambulatory medical care, can also point the way for us. There is no fundamental justification for keeping these two elements of medical care delivery separated. Finally, it should be evident to us that our health care delivery system should not try to maintain a "cottage industry" approach to medical care. Despite British attempts to preserve the traditional one doctor-one office-one patient idea, pressures have become too great to resist and the structure is moving toward localized group practices.

In summary, Britain's experience highlights the need for us to apply our managerial and marketing expertise to the delivery of health care, the need to amalgamate all health care services, and—perhaps most important—the need to profane some sacred cows in the pastures of American medicine.

Refer to: Strunk HK: Patient attitudes toward physician's assistants (The Health Care Team). Calif Med 118:73-77, June 1973

Patient Attitudes Toward Physician's Assistants

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A study was conducted in urban Los Angeles to assess patient acceptance of the use of physician's assistants. Data collection was facilitated by the development of an attitude scale and responses were analyzed to determine differences between various socioeconomic stratifications. With a few exceptions, acceptance was highest among non-married middle-class respondents who have had some exposure to college. As to the perceived complexity of procedures a physician's assistant might perform, 91 percent of all respondents would not object to injections administered by a physician's assistant, but this tolerance diminishes to 34 percent in the case of first examination of a patient by a physician's assistant if there appeared to be a serious head injury.

THE RECENT ARRIVAL of the physician's assistant on the medical scene has produced a concern about his acceptance by the public, but there remains a paucity of empirical data. While the number of practicing physician's assistants is relatively small, there are at least 22 operational programs in the United States striving to meet perceived paramedical manpower needs. Training aims and guidelines are established by the medical community to produce a new type of worker to bolster the ranks of medical personnel in the delivery of health care. It is to be hoped that such a worker will be acceptable to the patient—but much of this planning has been done with little patient input into the problem. Besides acceptance by other members of the health team, the question of patient acceptance of the physician's assistant obviously is an important one.

Estes and Howard[1] expressed the opinion there is little doubt that physician's assistants will be accepted by patients and that they can effectively

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extend the ability of the physician and allow him to see more patients. In addition, the physician's assistant is viewed as a possible means of reducing health care costs.

Kadish and Long[2] expressed belief that quality of care will be a major factor in the acceptance of physician's assistants. Of all the reasons for resistance, the question of quality is perhaps the one of most controversy. Preliminary acceptance on the part of the patient may be achieved by the implied acceptance of the assistant by the physician who employs him but, following that, the physician's assistant will be judged on his own merit.

Litman[3] sampled 253 households in Minnesota and Iowa to assess the potential willingness of rural residents to permit specially trained former medical corpsmen to provide various medical services under the supervision of a physician. Of the study population only 14 respondents lacked a regular family physician and 80 percent lived within 19 minutes of his office. He found 65.6 percent were willing to allow such trained assistants to care for their families, provided they were supervised by a licensed medical practitioner. However, 16 percent maintained that they would not. Acceptance was often based on the personal endorsement of the local family physician. The investigator inserted one very important word of caution: Any notion that such paramedical personnel are likely to be unequivocally accepted by the rural public seriously underestimates the latent resistance to be overcome.

The Litman study portends the need for information gathered from urban residents. The resistance among rural residents may also exist in the city. It would seem that public acceptance of the physician's assistant may well be contingent on the effectiveness of health education and the level of information possessed by the consumer.

Unlike rural areas faced with shortages of physicians, large urban areas do not manifest the same problem—with the possible exception of the decaying central city. Generally speaking, however, the city dweller has much more access to a wide range of medical services than does his rural counterpart. With need less evident, many urban areas—Los Angeles, for example—are unfamiliar with physician's assistants. In California, approval for physician's assistants training programs only recently has been given and the general public will not likely encounter a physician's assistant for some time to come. It is of further interest that television viewers currently are being exposed to a series dealing with the exploits of Los Angeles City Firemen trained as paramedics. Otherwise, there are pilot programs in the city which are using nurse midwives and nurse practitioners, but these have received little publicity.

Aims of the Study

A review of the literature reveals numerous gaps in our knowledge of the acceptability of the physician's assistant to the public. The best models of medical efficiency indicate that physician's assistants would be effective in triage and screening, performing non-complex procedures, and reserving only the most serious cases and disorders for the physician's unique skills. As yet, we do not know what the public's reaction might be to being screened out, thus not being judged a case to be called to the doctor's attention.

Another unexplored area of inquiry is the limits to treatment—that is, the degree of complexity—which the public would place on the practice of physician's assistants. From a training standpoint there are procedures for which physician's assistants may be well equipped and capable of performing, but an unanswered question is what the public will view as the limits of his competence.

A further aim of the study was to attempt to measure the attitudes of patients in relation to acceptance *vis-à-vis* socioeconomic stratification, and to determine whether a saving in time or money might be a condition of acceptance.

Method of Study

A 30-item attitude scale was developed, pretested and administered to 300 patients waiting for treatment at the UCLA Hospital Outpatient Clinic. Personal pronouns were used as much as possible in the questionnaire and situations were created with which the respondent might identify. It was hoped that administering the inquiry in a clinic's waiting room where a modicum of stress is present might contribute to the reliability of the responses. A Likert-type scale was used which permits respondents to reply on a continuum of "strongly agree" to "strongly disagree" with each statement. Statements were randomly ordered, weighted, and structured in such a way that agreement with some items and disagreement with others was favorable to the use of physician's assistants.

All patients presenting themselves to the UCLA Hospital Outpatient Clinic between the peak hours

TABLE 1.—*Frequency Distribution of Responses to Questions about Physician's Assistants*

	Strongly Agree	*Agree*	*Undecided*	*Disagree*	*Strongly Disagree*
1. Physician's assistants are OK for taking temperatures and weights, but my doctor should do all the rest	(1)* 18.0†	(2) 31.3	(3) 9.3	(4) 33.7	(5) 7.7
2. The best way to improve the Nation's health is to train more doctors	(1) 39.7	(2) 29.0	(3) 5.7	(4) 20.0	(5) 5.7
3. When I'm sick or injured, I don't want anyone to treat me who has less than an MD degree	(1) 27.7	(2) 23.7	(3) 11.3	(4) 30.7	(5) 6.7
4. A physician's assistant can do most of the things a doctor can do	(5) 3.0	(4) 30.7	(3) 23.7	(2) 35.0	(1) 7.7
5. Most children's diseases could be treated by a physician's assistant	(5) 3.7	(4) 22.7	(3) 12.7	(2) 47.0	(1) 14.0
6. Physician's assistants would probably be useful only in ghettoes or rural areas where they can't get doctors	(1) 2.7	(2) 15.0	(3) 8.0	(4) 51.3	(5) 23.0
7. The physician's assistant should be able to write and sign prescriptions for me	(5) 3.7	(4) 24.7	(3) 13.0	(2) 42.3	(1) 16.3
8. A physician's assistant could be used to screen patients to determine who actually should see the doctor	(5) 7.7	(4) 51.3	(3) 11.3	(2) 23.0	(1) 6.7
9. My doctor should allow his physician's assistant to treat whatever he can safely treat	(5) 16.0	(4) 64.3	(3) 9.3	(2) 6.7	(1) 3.7
10. Physician's assistants are OK for giving first-aid, but I still want to see the doctor when I come in to his office or clinic	(1) 21.0	(2) 46.0	(3) 14.3	(4) 17.7	(5) 1.0
11. The physician's assistant who used to be a military corpsman would probably be able to run a hospital emergency room without a doctor being there	(5) 4.0	(4) 22.3	(3) 18.0	(2) 41.3	(1) 14.3
12. Only the most serious cases should reach the attention of the doctor	(5) 6.3	(4) 16.7	(3) 7.0	(2) 54.0	(1) 16.0
13. I would be willing to accept the judgement of a physician's assistant on whether I should be seen by the physician	(5) 4.0	(4) 31.0	(3) 22.7	(2) 31.0	(1) 11.3
14. I wouldn't mind if my doctor had the physician's assistant give me an injection	(5) 21.0	(4) 70.0	(3) 5.3	(2) 2.3	(1) 1.3
15. If the physician's assistant treats me, it should cost me less money	(1) 11.3	(2) 36.0	(3) 25.7	(4) 24.0	(5) 3.0
16. Medical histories of an illness should only be taken by the physician who is going to treat me	(1) 12.7	(2) 27.0	(3) 9.3	(4) 44.7	(5) 6.3
17. I would be willing to see the physician's assistant if it would save me time	(5) 6.0	(4) 28.3	(3) 17.7	(2) 41.3	(1) 6.7
18. If a corpsman is good enough for our boys in Vietnam, he's good enough for me	(5) 6.3	(4) 25.3	(3) 24.3	(2) 36.7	(1) 7.3
19. Ex-military corpsmen should be willing to work as hospital orderlies unless they earn their MD degree	(1) 5.0	(2) 31.3	(3) 26.3	(4) 31.0	(5) 6.3
20. If I had some very personal problems bothering me, I would be willing to discuss them with my physician's assistant	(5) 4.7	(4) 34.3	(3) 16.3	(2) 34.7	(1) 10.0
21. Doctors should be the only ones allowed to sew up my cuts or wounds	(1) 14.7	(2) 29.7	(3) 10.3	(4) 38.3	(5) 7.0
22. If a physician's assistant, who used to be a military corpsman, could take care of my case according to my doctor, that would be OK with me	(5) 9.7	(4) 63.0	(3) 12.3	(2) 13.7	(1) 1.3
23. If I had a broken arm, it would be OK for the physician's assistant to set it	(5) 7.0	(4) 39.3	(3) 16.7	(2) 29.3	(1) 7.7
24. Doctors should delegate as much work as possible to the physician's assistant	(5) 6.7	(4) 46.0	(3) 21.3	(2) 23.0	(1) 3.0
25. Physicians spend too much time doing things that someone else could probably do	(5) 12.3	(4) 46.0	(3) 19.0	(2) 20.3	(1) 2.3
26. A physician's assistant should be able to take care of most conditions that doctors now are spending their time on	(5) 6.0	(4) 38.0	(3) 25.7	(2) 26.7	(1) 3.7
27. If I had fallen from a ladder and was bleeding from the nose and ears, it would be OK if the physician's assistant first examined me to see if I should be seen by the doctor	(5) 3.7	(4) 31.0	(3) 7.0	(2) 37.0	(1) 21.3
28. I would be willing to be treated by the physician's assistant if I felt that he knew what he was doing	(5) 11.0	(4) 59.3	(3) 11.7	(2) 17.0	(1) 1.0
29. The way to improve the Nation's health is to train more physician's assistants	(5) 20.0	(4) 47.3	(3) 16.7	(2) 12.7	(1) 3.3
30. If I were suffering from severe internal pain, I would not mind if the physician's assistant examined me first to see if he could give me what I needed	(5) 7.3	(4) 31.0	(3) 15.7	(2) 30.0	(1) 16.0

*1-5 represents assigned weights: 1, unfavorable attitude to 5, most favorable attitude.
†Figures expressed in percents, N=300.

of 9 and 10 a.m. on successive days were asked to participate in the survey. Each was approached by the researcher who explained that he was from the School of Public Health and conducting a study of innovative uses of medical manpower in which public opinion was needed. Anonymity was assured and each respondent was asked to read the first sheet of the questionnaire (which explained the physician's assistant concept and gave instructions for completing the questionnaire) and then to mark their responses. As they were completed they were collected by the researcher.

Results

Table 1 presents the responses of 300 patients to the attitude scale.

Sixty-two percent of the respondents were female and while means for their responses were significantly higher (that is, more accepting) on items 4, 7, 11, 18, 27 and 29, there was no statistical significance overall ($p<.05$).

Table 2 provides a breakdown by racial-ethnic origin among the sample. There was no significant difference ($p<.05$) in acceptance of the physician's assistant between the sub-groups. However, the means are presented for comparison.

An analysis of variance points to significant differences in the attitudes of acceptance when stratified by educational attainment (refer to Table 3). A rank ordering of means provides a ready comparison, but a word of caution is in order for the acceptance level indicated for respondents having less than seven years of education. The number of respondents was very small and, of the five, four were females. While there are no statistically significant differences in attitudes of acceptance between males and females, females consistently were more accepting. Acceptance also was consistently higher among those respondents who had had some exposure to college.

Acceptance by social position—social class—is significantly different. The Hollingshead Two Factor Index of Social Position[4] provides a measure to establish social position by the correlation of education and occupation. On the scale of 1 = highest class, and 5 = lowest class, the greatest acceptance was found to be in classes 2 and 3, or what would best be termed middle-class respondents. An analysis of variance of acceptance by social class is presented in Table 4.

Last, acceptance by marital status was significantly different. Non-married respondents were more accepting than married (or widowed) respondents. A rank ordering of acceptance may be seen in Table 5.

As Tables 3, 4 and 5 indicate, the greatest acceptance of the physician's assistant was found among non-marrieds and middle-class respondents who had had some exposure to college. It is persons of this group who most clearly see the role of the physician's assistant and the contribution he can make to the health team.

Responses to one of the attitude scale statements (Table 1) indicated that 67 percent of all respondents agreed that the way to improve the nation's health is to train more physician's assistants, which is a sharp contrast to the 41 percent in the first statement who believed that a physi-

TABLE 2.—*Distribution and Acceptance by Ethnic Origin*

	Number	*Percent*	*Mean*
American Indian	6	2.0	91.7†
Black	32	10.7	89.6
Caucasian	212	70.7	91.5
Mexican/American	28	9.3	88.5
Oriental	10	3.3	83.4
Other*	12	4.0	86.9
Total	300	100.0	90.6‡

*e.g., East Indian, Filipino, Indonesian, Samoan.
†As 90.0 is the midpoint of all possible responses, scores below would suggest unfavorable attitudes, while scores above would suggest favorable attitudes.
‡Mean for 300 respondents.

TABLE 3.—*Analysis of Variance—Acceptance by Educational Attainment*

	Number	*Mean*	*Std. Dev.*	*Maximum*	*Minimum*	*Rank Order*
Graduate professional training	13	89.6	20.8	126.0*	59.0	4
University graduate	36	93.4	17.7	145.0	67.0	3
Partial college (one year or more)	69	95.2	17.8	138.0	51.0	2
High school graduate	129	88.8	15.5	127.0	43.0	5
Partial high school (grade 10 or more)	36	87.9	15.1	121.0	50.0	6
Junior high school graduate	12	80.1	10.7	96.0	60.0	7
Less than 7 years of school	5	100.6	19.2	124.0	72.0	1

$F=2.63$ 6 d.f. ($F_{.95}=2.10$)
Possible range for total scores on 30 items = 30-150; 30 = unfavorable attitude, 150 = maximum favorable attitude.

TABLE 4.—*Analysis of Variance—Acceptance by Social Class**

Class	*Number*	*Mean*	*Std. Dev.*	*Maximum*	*Minimum*	*Rank Order*
1†	10	90.8	25.5	145.0‡	59.0	3
2	32	95.7	13.2	117.0	69.0	1
3	84	93.8	17.5	138.0	53.0	2
4	134	87.9	16.4	127.0	43.0	5
5	40	88.9	14.5	124.0	50.0	4
F=2.60		4 d.f.			($F_{.95}$=2.37)	

*As suggested by Hollingshead.
†Class 1 is the highest class.
‡Possible range for total scores on 30 items=30-150; 30=unfavorable attitude, 150=maximum favorable attitude.

TABLE 5.—*Analysis of Variance—Acceptance by Marital Status*

	Number	*Mean*	*Std. Dev.*	*Maximum*	*Minimum*	*Rank Order*
Married	169	89.8	16.8	145.0	43.0	4
Widowed ...	11	76.8	11.2	98.0	65.0	5
Separated ..	13	93.8	13.1	111.0	72.0	1
Divorced ..	42	93.7	20.1	138.0	51.0	2
Single	65	92.5	14.1	121.0	63.0	3
F=2.72		4 d.f.			($F_{.95}$=2.37)	

cian's assistant should be capable of doing something more than taking temperatures and weights. This phenomenon which is occurring might be termed "intratest learning" and is best illustrated by one patient's case. For background, the patient is a divorced Caucasian 41-year-old man, a high school graduate, employed as an aircraft maintenance man. A mean calculated for his first ten responses is 3.40; for the second ten responses, 3.40; third ten responses, 4.90 (on a scale of one to five). The indication here is that he shifted his attitude as he went, becoming more favorably disposed as the test progressed. This study is not designed to support the significance of this occurrence, but there is considerable evidence that this is not unusual.

Comment

The findings of this study indicate there are significant differences in acceptance of the physician's assistant which may be attributed to socioeconomic variables. This, in itself, is not surprising. Socioeconomic variables have a great deal to do with acceptance and choice in much of what we do on a daily basis. The important question that this study raises is whether people become more accepting as the level of information is increased. A glance at statement No. 28 on the attitude scale responses points to the willingness of two-thirds of the respondents to be treated by a physician's assistant *if they felt he knew what he was doing*. The implication is clear and the need now is to determine whether this is true, and, if so, what are the most productive means to bring about this end. The data generated by this study suggest that many people are ready for the appearance of the physician's assistant. The most pressing concern now seems to be how to inform and educate the public to prepare the remainder for his arrival.

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PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Director, State Department of Public Health

The Laetrile Hoax

THE PHYSICIAN who treats cancer is often confronted by a patient who demands treatment with Laetrile (amygdalin, an apricot pit derivative). The action of Laetrile on living cancers has been studied *in vitro,* in animals, and in man and in none of these studies has it shown any demonstrable anti-cancer effect.[1-3] Laetrile promoters claim that it is vitamin B-17, and that it prevents and controls cancer. They make a direct analogy between its supposed effects on cancer and those of insulin on diabetes.

No experimental or clinical evidence is offered to support any of these contentions except references to the Hunzas, a people in a remote area of Pakistan, or other allegedly cancer-free primitive peoples. However, a Japanese expedition to the land of the Hunzas reported that people there have cancer, as well as malnutrition, high infant mortality, and tuberculosis.[4]

Laetrile promoters also put forward the "unitarian" theory that all cancer is trophoblast. But none of the claimed Laetrile cures involve choriocarcinoma, a trophoblastic tumor which responds well to conventional therapy. The Cancer Advisory Council for the State Department of Public Health studied 190 cases of patients whose cancers were allegedly controlled or cured by Laetrile.[3,5] No case contained any valid evidence of cure or control attributable to Laetrile. Some of the patients still have their cancers; others had adequate conventional treatment in addition to Laetrile so that the effects of Laetrile cannot be determined, and still others, said to be cured, never had cancer at all.

In Mexico, Germany and elsewhere, some practitioners, unskilled in oncology, administer Laetrile to cancer patients. Reports of exacerbations of malignancy in patients whose metastatic malignancies were previously well-controlled by chemotherapeutic regimen have been called to our attention. Discontinuing the use of potent chemotherapeutic agents can, in itself, be detrimental. A San Francisco oncologist reports having personally observed 38 cancer patients who had received Laetrile; 36 are now dead and the other two are receiving other chemotherapeutic agents.

Furthermore, for reasons we do not understand, Laetrile given by mouth is 40 times as toxic as when administered parenterally, and also 40 times as toxic in cancerous as in normal animals. An ad hoc committee of oncologists, reviewing the data available in 1971, found that it would be dangerous to prescribe Laetrile even for investigational use because of the limited and unusual toxicity data.

Practitioners in Mexico and the United States who have been administering Laetrile have been relying on a human chorionic gonadotropin test of urine as an index of diagnosis and improvement, the so-called Anthrone test. This department has studied it and found it as accurate as flipping a coin.

Prescribing Laetrile or using the Anthrone test of cancer is a violation of the California Cancer Law. It is not only unprofessional conduct under the Business and Professions Code, but also illegal.

More detailed information regarding Laetrile and the other banned worthless cancer treatments (Hoxsey, Koch, Mucorhicin, Lincoln Staphage Lysate, Krebiozin, Bolen test) may be obtained from the Department of Public Health, Fraud Section, Bureau of Food and Drug, 2151 Berkeley Way, Berkeley, California 94704.

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5. KPIX, Jan 29, 1973

Information

CLINICAL CARDIOLOGY SERIES

Computers and Cardiovascular Medicine

JAMES W. COVELL, MD

Material Supplied by the American Heart Association

ALTHOUGH THE POTENTIAL of computer techniques in cardiovascular medicine has been recognized for some time, practical applications have become available only recently. Advances in technology coupled with rapid growth of a pool of personnel with special skills in biomedical computing have helped to propel computers to the forefront in cardiovascular diagnosis, patient care, and research at a cost that is no longer prohibitive.

There are two fundamental types of computers —analog and digital. An analog computer consists of linked networks of electronic components capable of analyzing and characterizing signals derived directly from physiological recordings. Analog computers are used to analyze and filter the electrocardiogram; recognize and record the frequency of ventricular premature contractions; calculate and record cardiac output, heart rate, systolic, diastolic, and mean arterial pressures. These devices have been effective in intensive care and coronary care units. However, their use is limited since they possess no capacity for memory and are thus unable to correlate a patient's current physiological status with other variables such as his past condition, or previous history or physicial findings. Their effectiveness can be enhanced by combination with the second type of computer—the digital computer.

Digital computers are complex, high speed, costly devices. They perform a wide variety of independent operations (additions, subtractions, multiplications) in microseconds; but they perform each operation one step at a time. Thus, they require a program that essentially "tells" the computer what step to take next and where, in circuitry, to store resultant information. Accordingly, digital computing requires first the electronic hardware—a computer—and, second, the software, that is, programs comprising instructions to the computer concerning a particular task. Each is equally essential to computer utilization.

Digital computation has been applied successfully to electrocardiographic diagnosis, patient monitoring, and the storage and retrieval of information derived from the patient's history and physical examination. Fortunately, existing hardware is now adequate for most tasks in these fields. Furthermore, numerous programs have been developed and tested, and are now commercially available.

Dr. Covell is Associate Professor of Medicine and Bioengineering, University of California, San Diego, School of Medicine.

Specific Applications

Electrocardiographic Diagnosis. During the past several years programs have been developed for electrocardiographic interpretation utilizing signals obtained either from standard 12-lead electrocardiographs or from vector cardiograph equipment. Naturally, some variation exists between a given physician's reading of an electrocardiogram and the computer's diagnostic analysis of the tracing. However, it is now generally accepted that computer analysis is effective in correctly classifying normal records and that good agreement between a human expert and the computer can be anticipated for most abnormal records as well. It is now possible to obtain electrocardiographic analysis by computer via ordinary telephone lines within minutes utilizing commercial services available in most areas. In some cases, computer recognition of abnormal tracings can be directly linked in order to initiate automatically additional expert consultation within a large center. Naturally, the computer cannot substitute for physician judgment based on the patient's previous electrocardiograms, history, or physical examination. In the assessment of these important diagnostic factors, as well as in the assessment of small variations in the electrocardiogram wave form, the computer cannot replace but can only supplement the skilled judgment of the physician.

Patient Monitoring. Perhaps the most rewarding and eventually most important application of computer electrocardiographic analysis will be in intensive care monitoring. It is well recognized that prompt treatment of bradycardia or ectopic

ventricular beats can lead to dramatic reductions in the mortality rate from acute myocardial infarction. Since programs are now available for on-line interpretation of arrhythmias and for on-line analysis of wave form, it is now possible to utilize computer diagnosis in the intensive care setting for on-line patient monitoring. Computer analysis of signals obtained with appropriate transducers can be used to monitor constantly not only the electrocardiogram, but also respiratory function, blood pressure, and other physiological functions. Programs have been devised which enable the computer to alert nurses or attending physicians whenever specified arrhythmias or alterations in hemodynamic or respiratory status occur. Computer systems for this purpose currently commercially available cost less than $10 per day per bed and can significantly supplement conventional monitoring techniques.

Discrete Data Analysis. Another area in which computers now contribute effectively to cardiovascular medicine is that of maintaining medical records. The extent of utilization of this important application has been disappointing. Theoretically, information entered in medical records can be classified and stored relatively easily with the aid of modern computing technology. Recent emphasis on the development of techniques necessary for direct computer-physician interaction and on utilization of problem-oriented medical records may help to facilitate more widespread applications in this area. Computer-physician interaction can be utilized as follows: the computer is programmed to flash a question on an oscilloscope screen. The physician responds in a yes or no fashion or by typing a response in ordinary English. The computer's questions continue, usually according to a "branching" logic pattern, similar to that employed by a physician obtaining a history. Thus, the computer might inquire whether chest pain had been present. An affirmative response would lead to additional questions concerning details including its radiation, intensity, duration and frequency. Depending on the response, the computer would ask additional questions to obtain further relevant data. By this means, data can be obtained for storage and retrieval in a logical format. This approach has been applied to storage and retrieval of information in nurses' notes, intake-output records, medication records, and physicians' history and physical examination reports.

Future Applications

Computing techniques will undoubtedly play an expanding role in cardiovascular medicine. Widespread utilization will probably occur first in the form of on-line monitoring in coronary care units and subsequently in electrocardiogram interpretation and large scale screening. Economic application of computing techniques to facilitate information storage and retrieval will ultimately be of considerable importance in effective maintenance and utilization of medical records for patient care as well as for investigation in cardiovascular medicine.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

CARSON, DONALD ALFONSO, San Francisco. Died April 14, 1973 in Sonoma, aged 77. Graduate of Columbia University College of Physicians and Surgeons, New York, 1925. Licensed in California in 1928. Doctor Carson was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

GARRETT, FRANKLIN H., Oxnard. Died November 25, 1972 in Costa Mesa of coronary sclerosis, aged 76. Graduate of the University of Arkansas School of Medicine, Little Rock, 1926. Licensed in California in 1928. Doctor Garrett was a retired member of the Ventura County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

HARDY, KENNETH LESLIE, Oakland. Died accidently April 28, 1973 when a tractor rolled over him at his Castro Valley ranch, aged 52. Graduate of Yale University School of Medicine, New Haven, 1946. Licensed in California in 1950. Doctor Hardy was a member of the Alameda-Contra Costa Medical Association.

HEINATZ, MARIE ANTISDEL, Oakland. Died April 7, 1973 in San Jose of heart disease, aged 88. Graduate of Jenner Medical College, Chicago, 1917. Licensed in California in 1922. Doctor Heinatz was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

HERRINGTON, EDWARD L., San Francisco. Died April 3, 1973 in San Francisco, aged 91. Graduate of the College of Physicians and Surgeons of San Francisco, 1906. Licensed in California in 1907. Doctor Herrington was a member of the San Francisco Medical Society.

HILL, HAROLD A., San Francisco. Died April 2, 1973 in San Francisco, aged 72. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Doctor Hill was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

HILL, LOWELL MARTIN, Redondo Beach. Died March 21, 1973 of leukemia, aged 38. Graduate of Stanford University School of Medicine, Palo Alto, 1960. Licensed in California in 1961. Doctor Hill was a member of the Los Angeles County Medical Association.

HOLCOMB, RUSSELL F., JR., Rancho Santa Fe. Died April 18, 1973 of injuries received in an automobile accident near La Paz, Mexico, aged 39. Graduate of the University of Virginia School of Medicine, Charlottesville, 1961. Licensed in California in 1963. Doctor Holcomb was a member of the San Diego County Medical Society.

JOHNSON, FLOYD W., Stockton. Died April 21, 1973 in Stockton, aged 64. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1952. Licensed in California in 1952. Doctor Johnson was a member of the San Joaquin County Medical Society.

KREUTZMANN, WALTER B., San Francisco. Died March 17, 1973 in Belmont, aged 61. Graduate of the University of Rochester School of Medicine and Dentistry, 1942. Licensed in California in 1943. Doctor Kreutzmann was a member of the San Francisco Medical Society.

LANGDON, ERLE EDWARD, Santa Monica. Died March 31, 1973 of cerebrovascular accident, in Santa Monica, aged 78. Graduate of the University of Colorado School of Medicine, Denver, 1920. Licensed in California in 1928. Doctor Langdon was a member of the Los Angeles County Medical Association.

LANGSTON, EUGENE D., JR., Torrance. Died March 29, 1973 of heart disease, in Torrance, aged 63. Graduate of Emory University School of Medicine, Atlanta, 1942. Licensed in California in 1946. Doctor Langston was a member of the Los Angeles County Medical Association.

NOWLIN, OWEN E., San Diego. Died April 10, 1973 in La Mesa, aged 72. Graduate of the University of Illinois College of Medicine, Chicago, 1925. Licensed in California in 1925. Doctor Nowlin was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

RUKKE, RAYMOND VICTOR, Monterey. Died March 27, 1973 in Monterey, aged 64. Graduate of the University of California Medical School, Berkeley-San Francisco, 1935. Licensed in California in 1935. Doctor Rukke was a retired member of the Monterey County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

VON HUNGEN, ADOLPH PHILIP, Escalon. Died April 8, 1973 in Stockton, aged 68. Graduate of the University of Oregon Medical School, Portland, 1927. Licensed in California in 1929. Doctor Von Hungen was a member of the Stanislaus County Medical Society.

WAKEFIELD, JOHN M., Sutter Creek. Died November 13, 1972 in Sacramento of arteriosclerosis, aged 75. Graduate of Harvard Medical School, Boston, 1927. Licensed in California in 1927. Doctor Wakefield was a retired member of the Sacramento County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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